Adenosine Deaminase 2: from the spectrum of phenotypes to the diagnosis and treatment

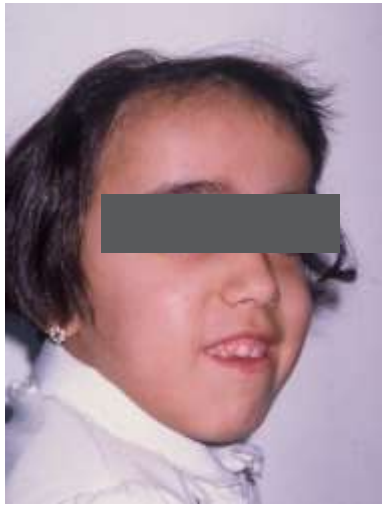
Gustavo C. Santo

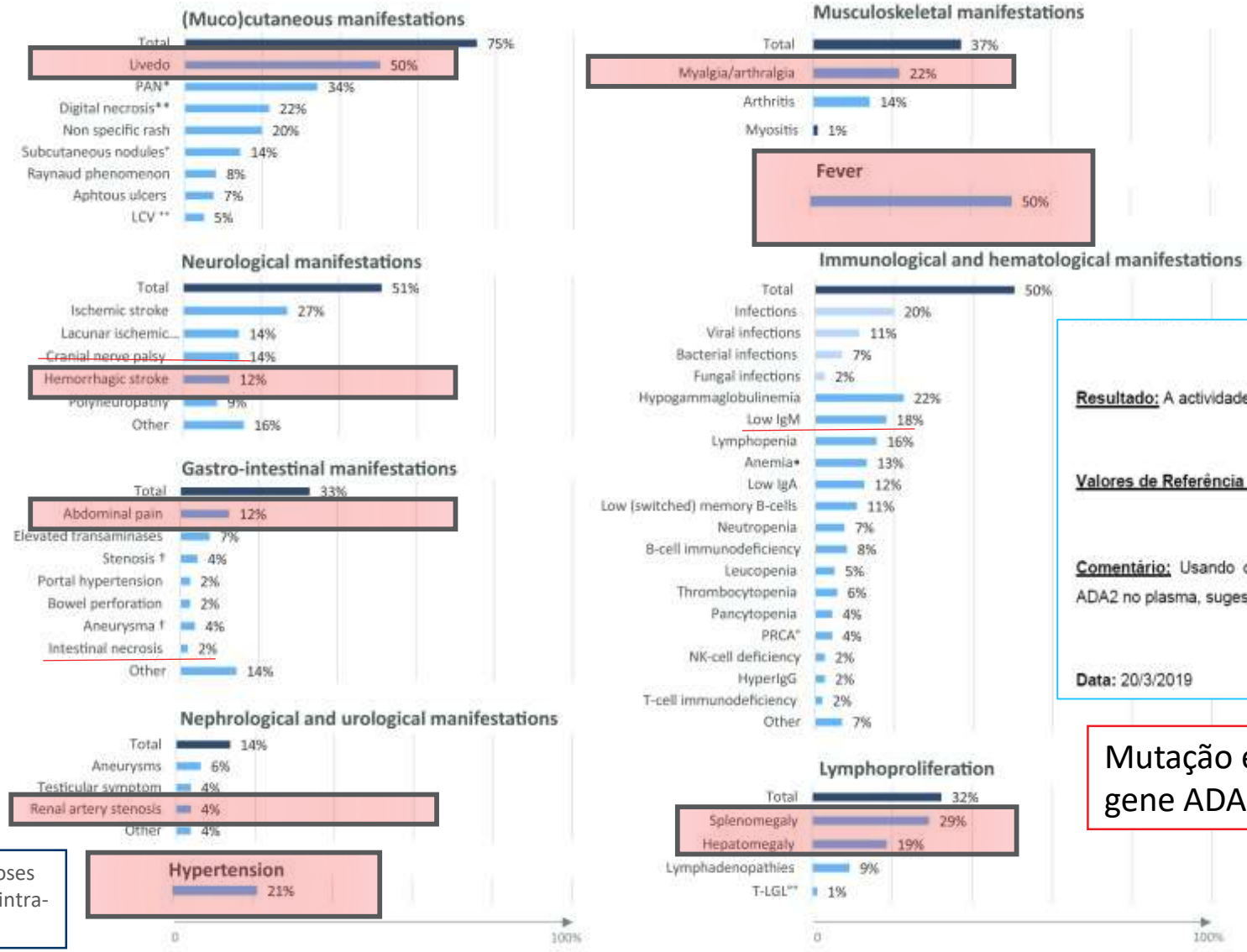
September 2020

Objetives

- ❑ Describe the clinical presentation and the expansion of the spectrum phenotypes
- ❑ Pathophysiology
- ❑ Diagnosis: genetics and plasma ADA2 activity
- ❑ Treatment

Clinical manifestations in DADA2





*Polyarteritis Nodosa; **Digital necrosis including skin ulcers; *Subcutaneous nodules including erythema nodosum; **Leucocytoclastic vasculitis; †Mesenteric, Celiac or Hepatic artery; •Including Diamond Blackfan anemia and hemolytic anemia; *Pure Red Cell Aplasia; **T-cell Large Granular Lymphocytic infiltration of the bone marrow;

Resultado: A actividade da ADA2 no plasma foi de **0,0 U/L**.

Valores de Referência do Laboratório: >5.15 U/L

Comentário: Usando o método acima referido, foi detectada uma **actividade nula** de ADA2 no plasma, sugestiva de deficiência de ADA2 (DADA2).

Data: 20/3/2019

Mutação em homozigotia Tyr453Cys no gene ADA2

Angiografia renal: múltiplas estenoses e dilatações na pequenas artérias intra-renais

Clinical manifestations in DADA2

Two cases of ADA2 deficiency presenting as childhood polyarteritis nodosa: novel *ADA2* variant, atypical CNS manifestations, and literature review

Sara Ganhão[1] · Graça Barros Loureiro[2] · Diana Rita Oliveira[3] · Rúben dos-Reis-Maia[4] · Francisca Aguiar[5] Rita Quental[6] · Carla Moura[6,7,8] · João Luís Barreira[9] · Mariana Rodrigues[5] · Iva Brito[5,7]

Received: 16 January 2020 / Revised: 25 May 2020 / Accepted: 29 May 2020

- Abdominal pain
- Distension and absence of bowel movements
- Underwent colostomy and ileostomy constrution due to ileal stenosis
- Histology examination of jejunum and ileum revealing necrotizing inflammation of medium and small-sized arteries

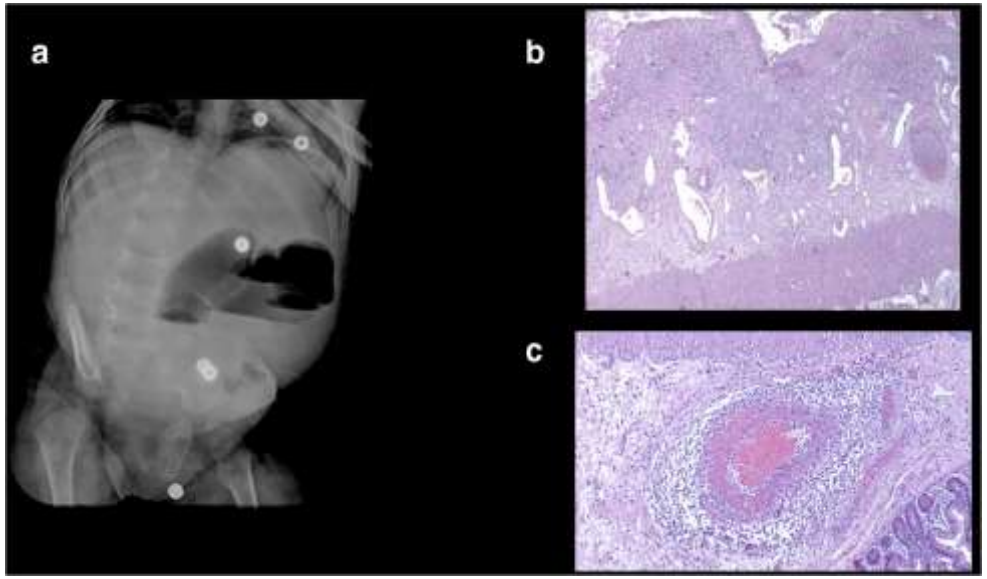
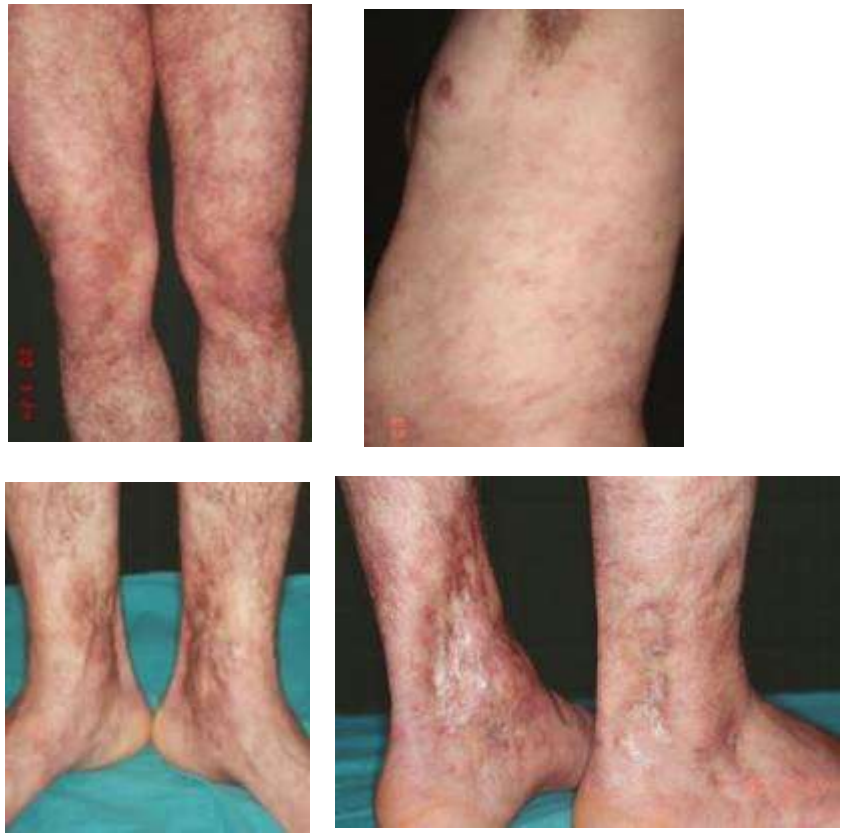


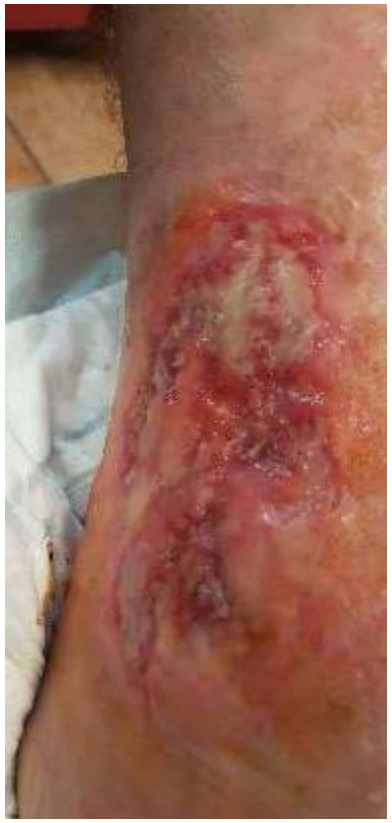
Fig. 3 Abdominal X-ray showing air-fluid levels (**a**). Pathologic examination of jejunal artery revealing necrotizing inflammation of medium- and small-sized arteries (**b**, **c**)

Clinical manifestations in DADA2

Skin Manifestations in our cohort

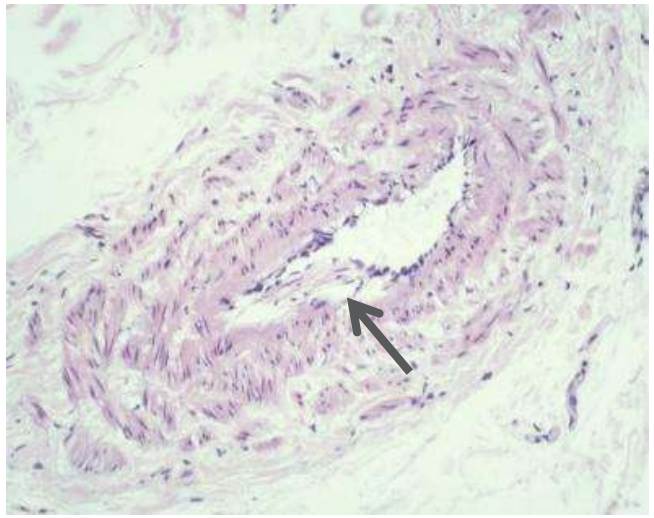


2002

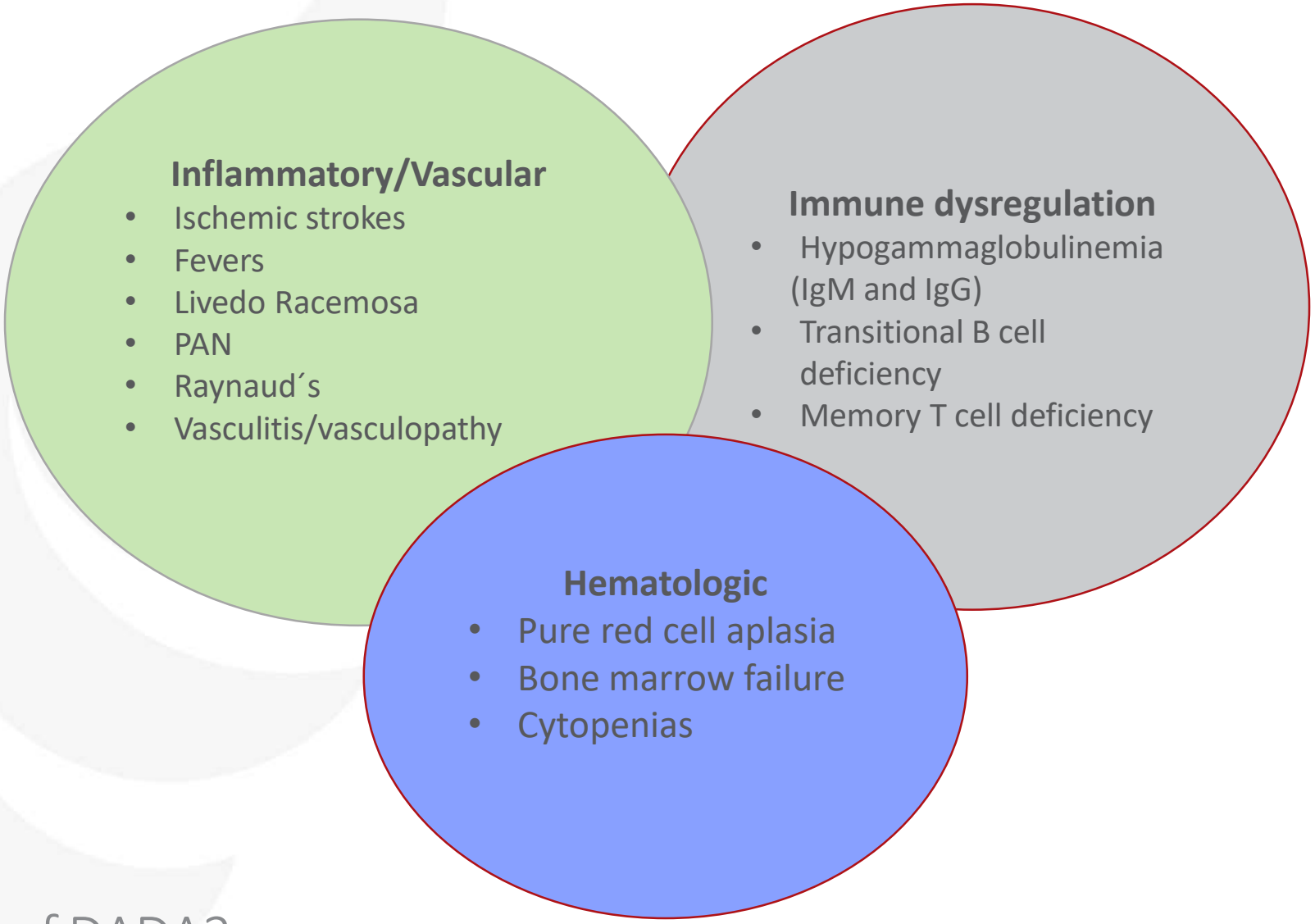


2018

Skin Biopsy



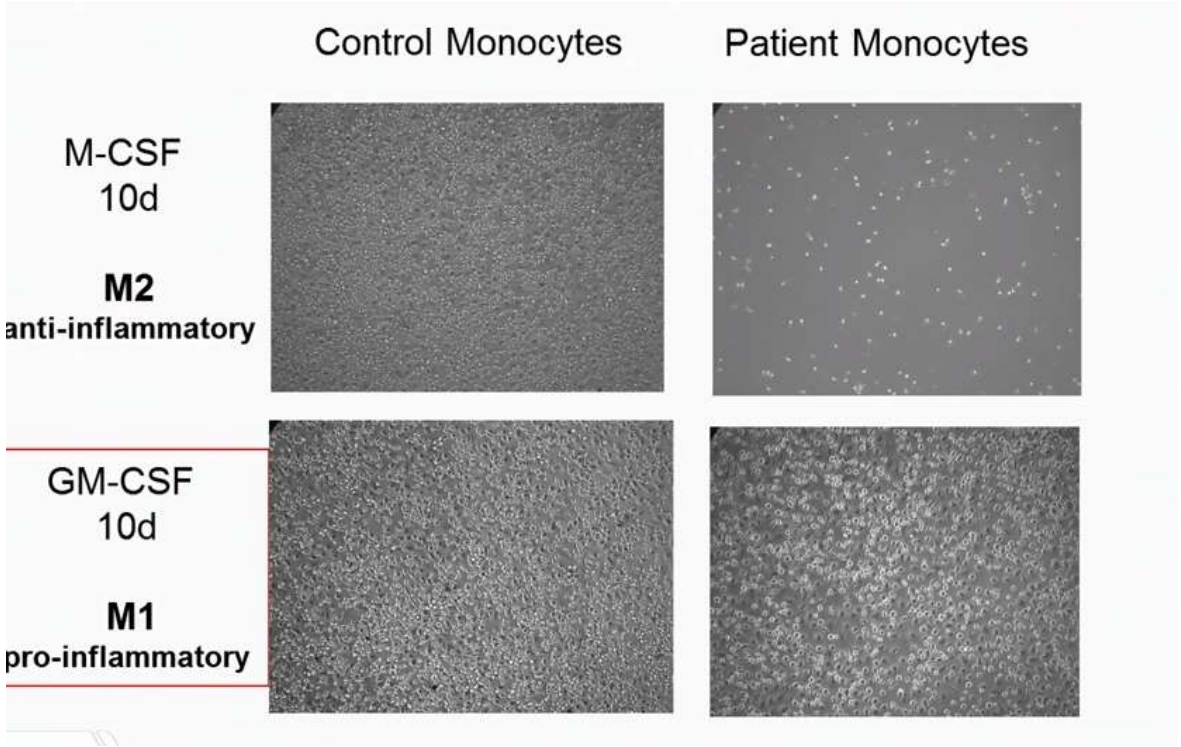
DADA2 in 2020



Expanding Phenotype of DADA2

Pathophisiology of DADA2

Impaired M2 macrophage differentiation in DADA2

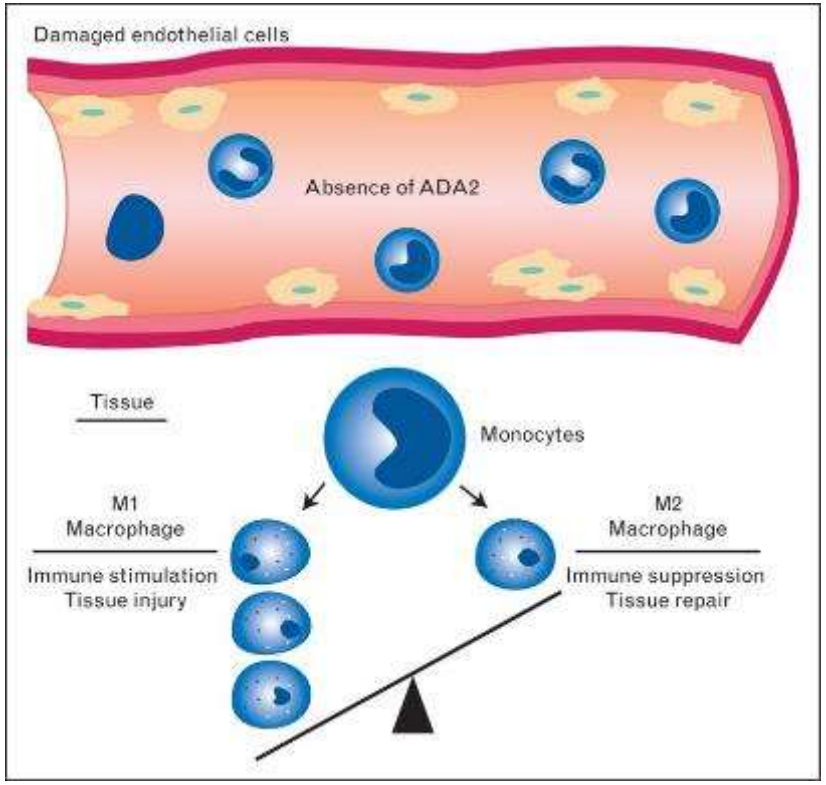


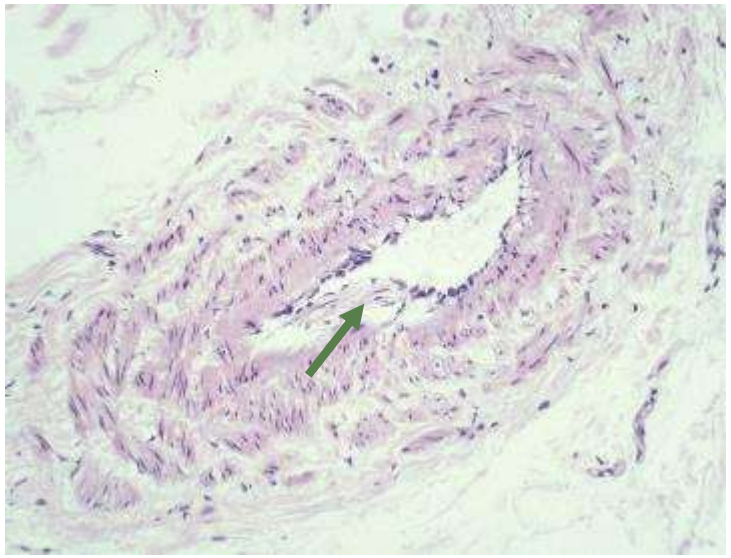
ADA2:

- works as a growth factor
- is important for the differentiation of monocytes into macrophages

Zhou et al. NEJM 2014

Pathophisiology of DADA2





Skewing toward proinflammatory M1 macrophages leads to accumulation of proinflammatory cytokines and tissue injury.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mutant Adenosine Deaminase 2 in a Polyarteritis Nodosa Vasculopathy

Elkan *et al.* NEJM 2014

Cat Eye Syndrome Chromosome Region, Candidate 1 (CECR1) gene encoding Adenosine Deaminase 2 (ADA2)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early-Onset Stroke and Vasculopathy Associated with Mutations in ADA2

Zhou *et al.* NEJM 2014

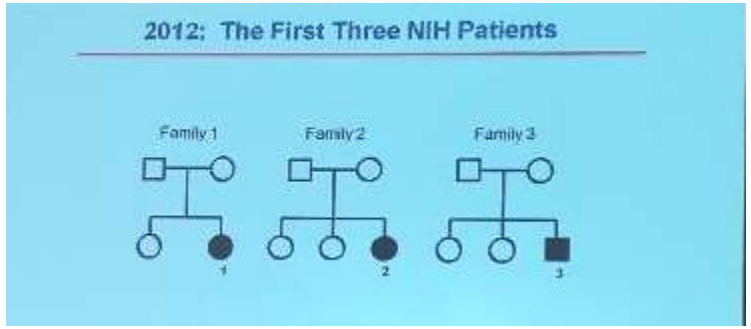
2014

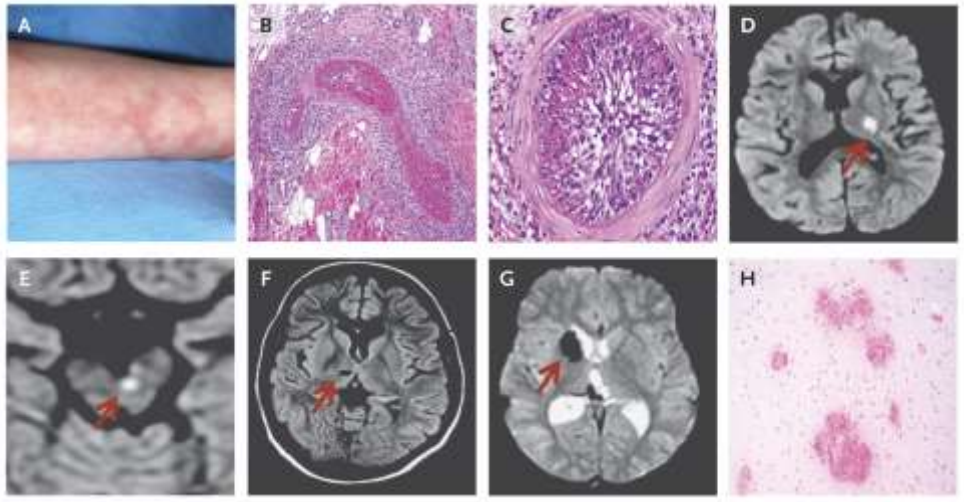
The NEW ENGLAND JOURNAL of MEDICINE

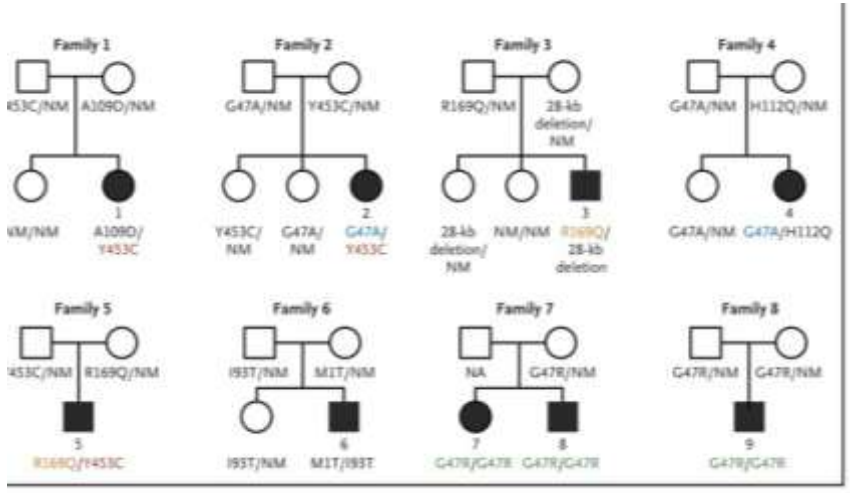
ORIGINAL ARTICLE

Early-Onset Stroke and Vasculopathy Associated with Mutations in ADA2

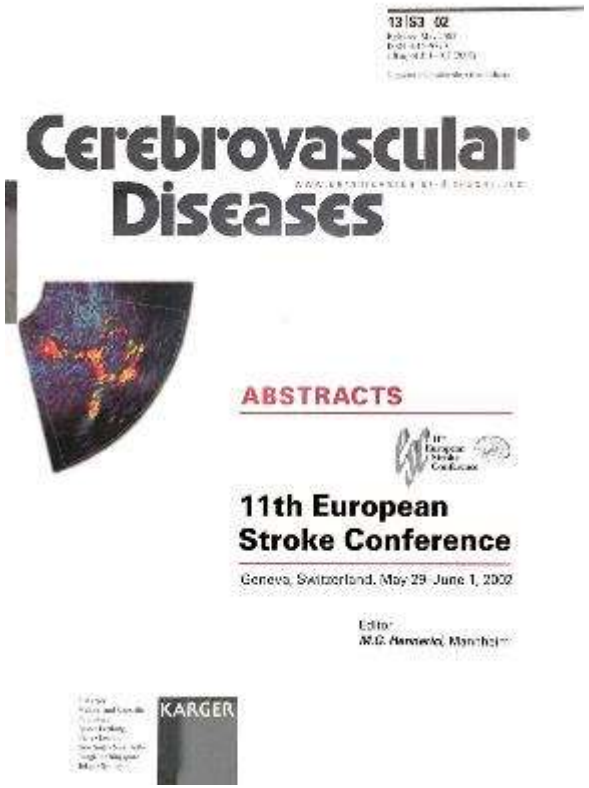
Q. Zhou, D. Yang, A.K. Ombrello, Andrey V. Zavialov, C. Toro, Anton V. Zavialov, D.L. Stone, J.J. Chae, S.D. Rosenzweig, K. Bishop, K.S. Barron, H.S. Kuehn, P. Hoffmann, A. Negro, W.L. Tsai, E.W. Cowen, W. Pei, J.D. Milner, C. Silvin, T. Heller, D.T. Chin, N.J. Patronas, J.S. Barber, C.-C.R. Lee, G.M. Wood, A. Ling







2002/May…



O215 Genetic Disorders

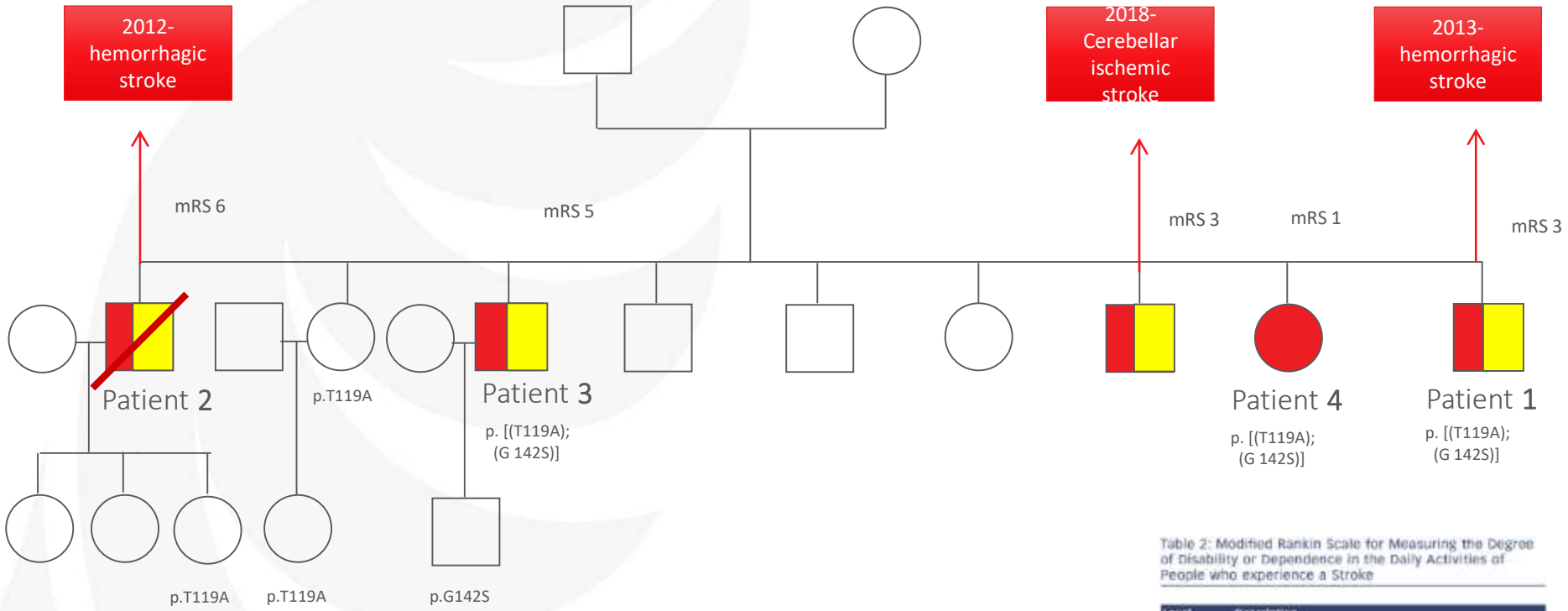
FAMILIAL SNEDDON'S SYNDROME: Clinical, dermatologic, hematologic and radiographic findings

G.C. Santo, R. Mascarenhas, A. Geraldo, M. Gonçalo, M.A. Ferro
Hospitais da Universidade de Coimbra, Portugal

The authors present the clinical, dermatologic, hematologic and neuroradiographic findings of three brothers from one family with Sneddon's Syndrome (SNS). Their non-consanguineous parents have 6 sons and 3 daughters. Of these, 6 have Livedo Racemosa (LR), 3 of them without history of cerebrovascular events. Patient 1, 28 years old, male, was admitted at the Neurology Department in January 2000 with a left lacunar stroke. Patient 2, 42 years old, male, was admitted in February 2000 with a right lacunar stroke. Patient 3, 37 years old, male, had two intracerebral hemorrhages (1986 and 1997). The authors also examined one sister, 31 years old (Patient 4), with LR but no cerebrovascular disease. All four have long lasting LR with an open reticular pattern, localized mainly in the lower limbs extending to the trunk and upper limbs. Antiphospholipid antibodies and lúpus anticoagulant were negative in all after repeated screenings. Skin biopsy disclosed, only in Patient 2, incomplete occlusion by fibrinoid thrombi and partial endothelium detachment in dermo-hipodermic blood vessels. Cerebral CT scan, MRI and angiography were performed in all. The association of LR and cerebrovascular disease was described by Sneddon in 1965. Most cases are sporadic with rare familial cases. The present one represents the largest number of siblings ever described and suggests a dominant autosomal transmission with incomplete penetrance and variable expression. The relationship between SNS and Antiphospholipid Syndrome is controversial. This case seems to support the concept that SNS is a well defined independent nosological entity.It also shows that, although rare, these patients may present with an intracerebral hemorrhage.

Evolution: the natural history of one family

2018



Livedo racemosa and skin lesion in the lower limbs

Stroke

Table 2: Modified Rankin Scale for Measuring the Degree of Disability or Dependence in the Daily Activities of People who experience a Stroke

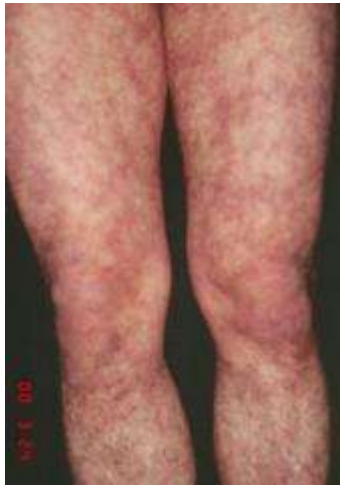
Level	Description
0	No symptoms
1	No significant disability, despite symptoms; able to perform all usual duties and activities
2	Slight disability; unable to perform all previous activities but able to look after own affairs without assistance
3	Moderate disability; requires some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requires nursing care and attention

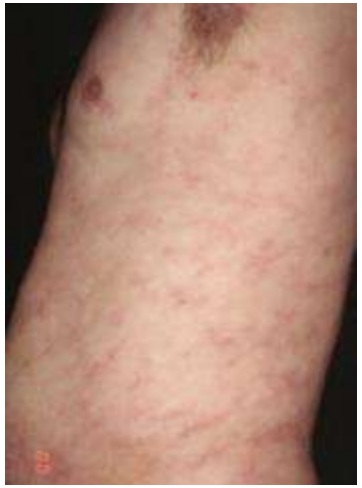
Adapted from Rankin, 1957 and van Swieten et al., 1988

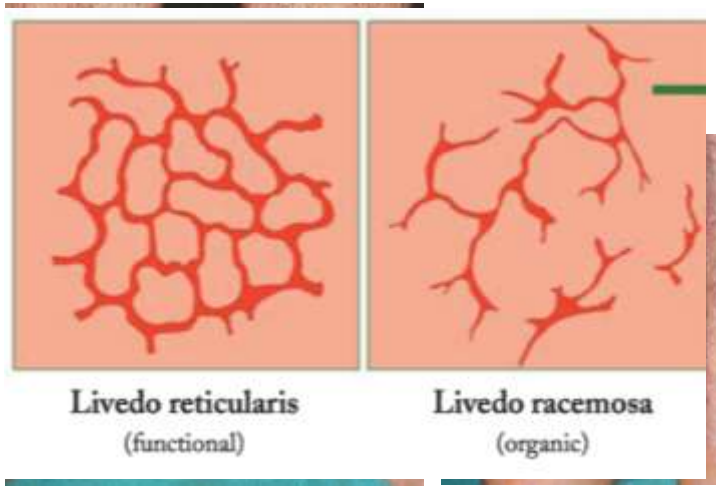
Patient 2

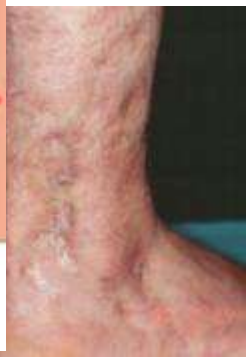
Male, right lacunar stroke when he was 29 years-old

Since the age of 16:
- *livedo racemosa* on lower limbs and trunk;
- Recurrent and seasonal leg ulcerations, on the distal part of the legs









Diagnosis

- Autosomal recessive loss-of-function mutation in ADA2 gene

- High clinical suspicion
- Check for consanguinity!

- Plasma ADA2 activity
- Genetic testing

DADA2 in 2020

- Not a rare disorder
- Over 400 patients reported worldwide
- 152 confirmed at NIH
- 8 in Portugal (and 19 heterozygous…)
- Estimation: 4.3 in 100,000 people have biallelic, predicted damaging mutations in ADA2
- Missing patients from Africa, India, China, Japan, Australia and someof European countries

Genetics of DADA2

Highly polymorphic gene, over 300 variants in the coding part of the gene

Over 70 pathogenic variants, mostly missence

Copy number variations (CNVs): deletions/duplications

Non-coding mutations (splice variants)

Not all rare novel variants are associated with low ADA2 activity

genotype-phenotype correlations under investigation

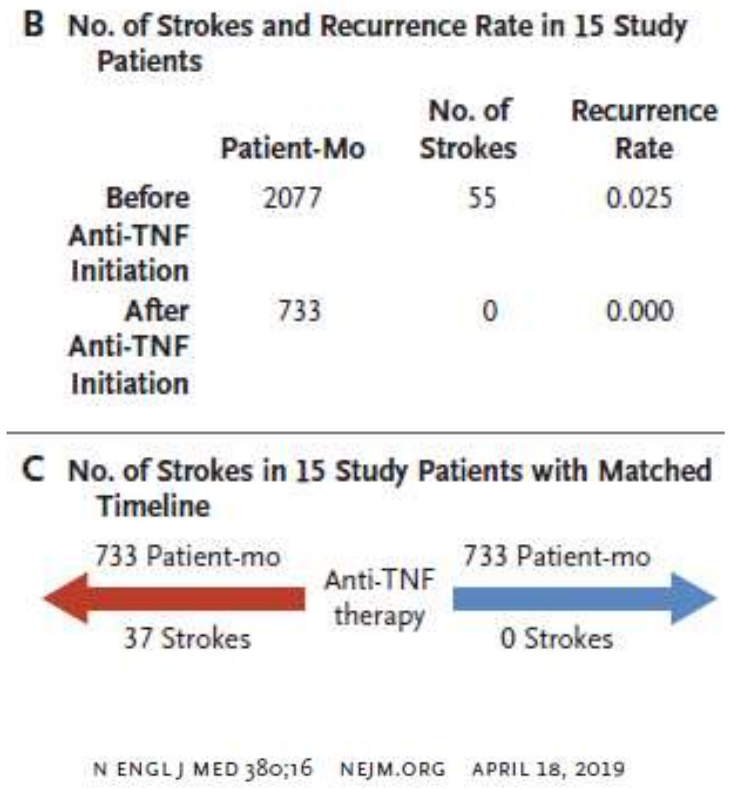
Clinical variability seen in families and in patients with the same genotype

Reduced penetrance (modifying genetic or environmental factors)

Therapies in DADA2 (no formal trials yet)

❖**TNF inhibitors** (etanercept, infliximab, adalimumab, golimumab, thalidomide)

- Are very effective in controlling inflammatory phenotype and in prevention of stroke
- Should be initiated ASAP
- IL-1 inhibitors are not efficacious
- Discontinue aspirin and/or anticoagulants
- May not be effective in patients with immunological/hematological presentation
- Some reports showed that it may help with lymphopenia/ hypogammaglobulinemia



B No. of Strokes and Recurrence Rate in 15 Study Patients

	Patient-Mo	No. of Strokes	Recurrence Rate
Before Anti-TNF Initiation	2077	55	0.025
After Anti-TNF Initiation	733	0	0.000

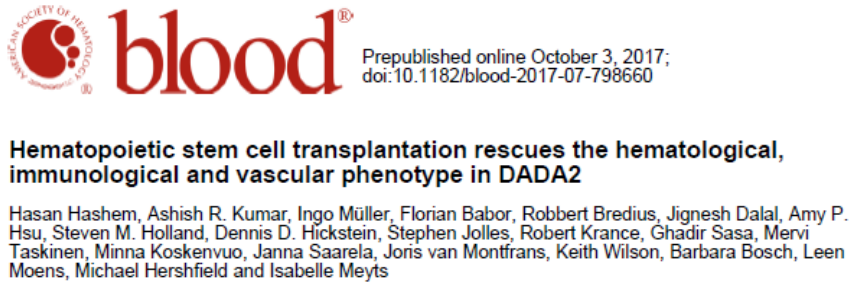
C No. of Strokes in 15 Study Patients with Matched Timeline

Therapies in DADA2

- TNF inhibitors (etanercept, infliximab, adalimumab, golimumab, thalidomide)

- Hematopoietic Stem Cell Transplantation

15 patients



Key points:

- HSCT represents and effective and definitive treatment for DADA2 (but important caveats)
- Normalized plasma ADA2 activity
- HSCT can cure the immunological, hematological and vascular phenotype of DADA2 with 100% survival at a median follow-up of 18 months

- Gene therapy (clinical trials expected in 6-8 years)
- Enzyme replacement (less likely)

Summary

DADA2 is a potentially fatal monogenic loss-of-function disease described in 2014;

Since the original description of childhood vasculitis, more than 400 cases have been reported, greatly expanding the phenotype;

Given the pleiotropic presentations and different age of onset, the disease span multiple different specialities and is probably underdiagnosed;

The pathophysiology is largely unknown and the diagnostic accuracy of more affordable biochemical testing are being established.

TNF inhibitors are effective in suppressing systemic inflammation; probably not in other phenotypes

Summary

Estudo genético para DADA2 é ainda o gold standard mas:

- Perante a suspeita clínica deve pedir-se o doseamento da actividade enzimática da ADA2 em laboratório credível (e se diminuída solicitar estudo genético);
- Evitar – sempre que possível - estudos genéticos em painel
- Participar na construção de uma base de dados nacional destes doentes