III Curso de Reumatologia Pediátrica para Médicos Internos
10, 11, 17, 18 de setembro 2020

CHUC HOSPITAL PEDIÁTRICO

DÉFICE DE ADENOSINA DEAMINASE 2

UM DIAGNÓSTICO QUE DEMOROU 28 ANOS

Jorge Rodrigues[1], Clara Pardinhas[2], Gustavo Cordeiro Santo[3,4], António Jorge Correia[5], Manuel Salgado[1]

[1] Unidade de Reumatologia Pediátrica, Hospital Pediátrico, CHUC
[2] Serviço de Nefrologia, CHUC
[3] Serviço de Neurologia, CHUC
[4] Centro de Neurociências e Biologia Celular, UC
[5] Unidade de Nefrologia Pediátrica, Hospital Pediátrico, CHUC

03.05.1991 | I: 3.5 meses de idade

SU – HP:
Paralisia facial periférica à direita – D0
Vómitos + irritabilidade – D7
Má progressão ponderal desde o nascimento

EO – **PA 176/123 mmHg**; palidez; **sopro craniano audível;** AC com sopro sistólico grau II/VI mais audível no BEE; sem organomegálias; pulsos distais palpáveis e simétricos; de resto sem alterações

Internamento no CIPE por **crise hipertensiva**

Gestação, parto e período neonatal sem intercorrências

Pais primos 3º grau

Mãe com diagnóstico de **AIJ sistémica** e posteriormente **doença de Behçet**

Avó paterna com DRT por HTA

03.05.1991 | I: 3.5M

Investigação etiológica realizada:

Hb 9.0 g/dl (VGM 69 fL, HCM 21.7 pg), WBC 16 600/uL (N 7 300/uL, L 8 700/uL), P 649.000/uL
VS 32 mm/h, pCr 2.7 mg/dl
Ureia 2.9 mmol/L, creatinina 104 µmol/L, restante bioquímica N
Proteinúria não nefrótica
Renina ativa > 250 ng/ml/h (↑), aldosterona 1157 ng/dl (↑), VMA 4.5 mg/g Cr (N)

Radiografia tórax: ICT aumentado
Ecocardiograma: sem alterações

RM-CE: N

Angiografia renal: estenose e dilatações múltiplas nas pequenas artérias intrarenais, sobretudo à esquerda – HTA renovascular

Cintigrama DMSA: hipocaptação a nível do RE com função diferencial RE 38% / RD 62%

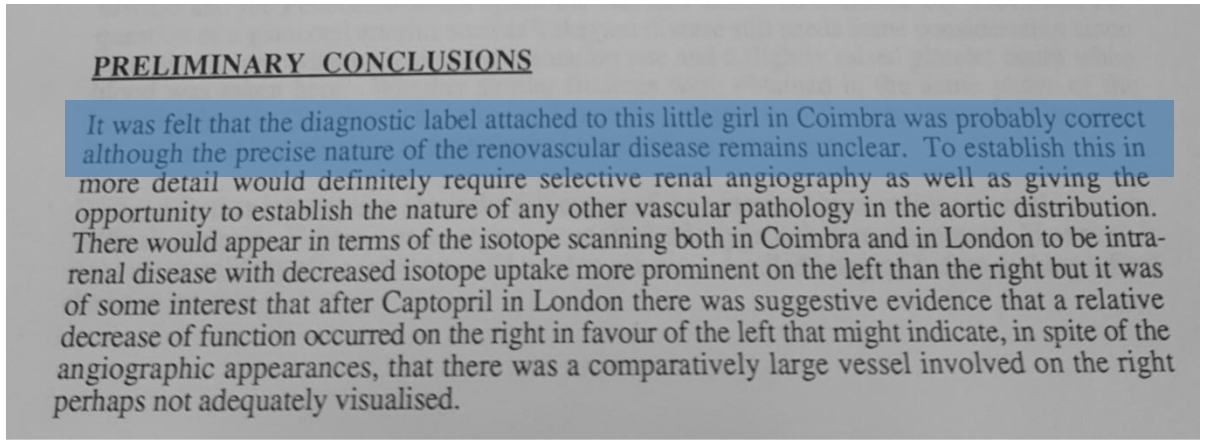
09.07.1991 | 30.03.92 (6 e 14M)

Observada em 2 ocasiões na Nefrologia do *The Hospital for Sick Children* em Londres

Repetiu estudo cintigráfico e realizou angiografia carotídea e aórtica e angiograma cerebral bicarotídeo (com HMPAO) que **não revelaram sinais de vasculopatia**

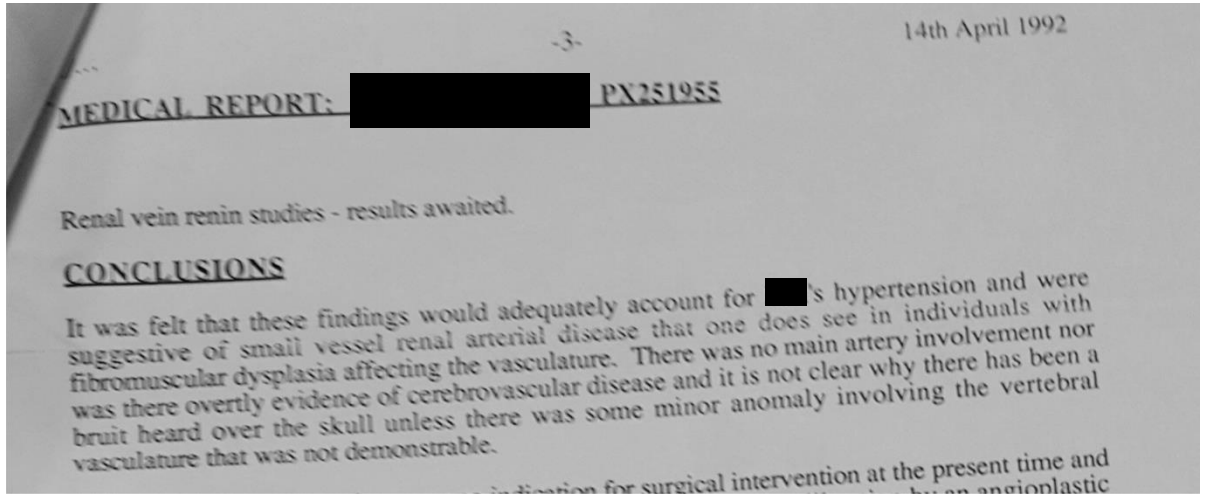
HTA renovascular

Causa X



PRELIMINARY CONCLUSIONS

It was felt that the diagnostic label attached to this little girl in Coimbra was probably correct although the precise nature of the renovascular disease remains unclear. To establish this in more detail would definitely require selective renal angiography as well as giving the opportunity to establish the nature of any other vascular pathology in the aortic distribution. There would appear in terms of the isotope scanning both in Coimbra and in London to be intra-renal disease with decreased isotope uptake more prominent on the left than the right but it was of some interest that after Captopril in London there was suggestive evidence that a relative decrease of function occurred on the right in favour of the left that might indicate, in spite of the angiographic appearances, that there was a comparatively large vessel involved on the right perhaps not adequately visualised.



-3- 14th April 1992

MEDICAL REPORT: [redacted] PX251955

Renal vein renin studies - results awaited.

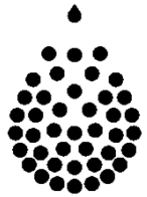
CONCLUSIONS

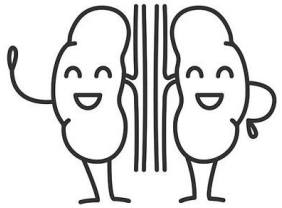
It was felt that these findings would adequately account for [redacted]'s hypertension and were suggestive of small vessel renal arterial disease that one does see in individuals with fibromuscular dysplasia affecting the vasculature. There was no main artery involvement nor was there overtly evidence of cerebrovascular disease and it is not clear why there has been a bruit heard over the skull unless there was some minor anomaly involving the vertebral vasculature that was not demonstrable.

...dication for surgical intervention at the present time and ...by an angioplastic

Manteve seguimento em consulta de Nefrologia Pediátrica:

Exantema intermitente
desde 06.01.92 (2A)





Anemia microcítica hipocrómica refratária a ferro
desde 21.09.94 (3A)

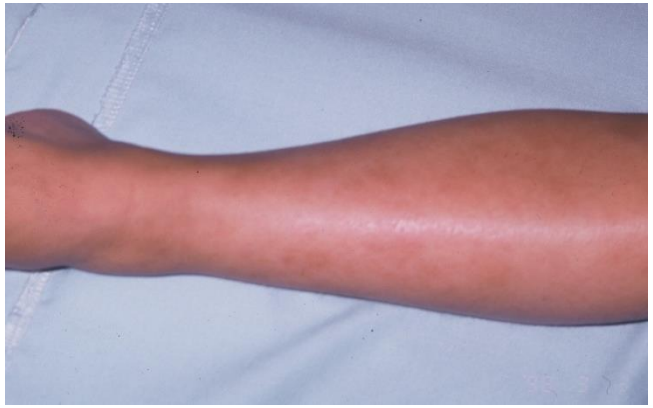
Proteinúria não nefrótica
persistente > 6A

Ataxia e nistagmo recorrente
4-5A

Febre recorrente
desde 01.09.1997 (6A)

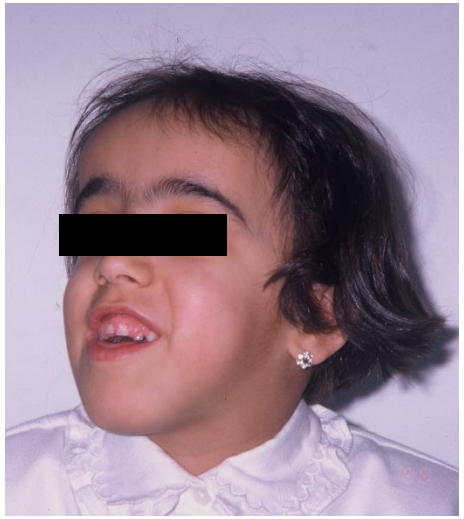
30.12.1997 | I: 7A

Febre vespertina, inicialmente não diária → diária 95 dias
Episódios de curta duração de **dor abdominal** periumbilical
Livedo reticular vs. racemoso
Hepatoesplenomegalia palpável
Poliartralgias recorrentes das grandes articulações



AIJ sistémica?

URP – HP - CHUC



Artrite TT direita + hipocratismo digital (= pai)

Episclerite OD

Fenómeno Raynaud

"Exantema" fixo nas pernas → *Livedo reticularis*

30.12.1997 | I: 7A

- Serologias para CMV, EBV, HIV, *Mycoplasma, Chlamydia, Brucella*, *Bartonella, Leishmania, Leptospira, Borrelia, Candida, Cryptococcus;* prova tuberculínica; pesquisa *Plasmodium*
- SACE, FR, TASO, ANA, anti-dsDNA, ANCA, ENA *screen*, anti-fosfolípidos
- Proteinograma; C3, C4, CH50; estudo trombofilias; ceruloplasmina
- Biopsia cutânea

Infecioso?

Inflamatório?

Neoplásico?

Metabólico?

- IgA 1.0 (N), IgG 4.6 (N↓), **IgM 0.3 (↓)**
- **HLA B27 positivo**
- Estudo IDP: “**diminuição** da **atividade quimiotáxica** dos **neutrófilos**; défice de expressão de CD15 nos leucócitos”
- TAC toracoabdominal: “**bronquiectasias** do tipo **cilíndrico** […] múltiplos **gânglios mesentéricos** e para-aórticos aumentados de volume”

PAN sistémica?

Síndrome Blau?

Outra causa?

25.05.1999 – 01.06.1999 (8A)

SU – HP:
Dor abdominal periumbilical + 2 episódios de **melenas**
Hb 6.6 g/dl (na admissão) → Transfusão de 1 UCE

Laparatomia exploradora: "adenite mesentérica"
Biopsias gânglios mesentéricos – sem alterações

Internamento no CIPE e posteriormente no SPM – <u>HDB sem etiologia conhecida</u>

Inconclusivo

Ecografia AP (25.05.99): sem alterações

Cintigrama para pesquisa de divertículo Meckel (25.05.99): negativo

Colonoscopia e TEGD (30.05.99): sem alterações

21.03.2000 – 19.04.2000 (9A)

SPM-HP-CHUC: internamento por **febre prolongada** (> 3 semanas)

- VS 125 mm/h, pCr 25 mg/dl e ferritina 1.252 ng/ml à admissão
- Esplenomegalia com imagem cavitada do baço documentada ecograficamente
- Múltiplos abcessos renais documentados ecograficamente
- Estudo ecocardiográfico sem alterações

D1 internamento → cefaleias + vómitos + convulsão + HTA
TC-CE: AVC hemorrágico parietoccipital esquerdo
RM-CE: "Cavernoma" parietal posterior esquerdo → cirurgia a 11.07.00
Recuperação neurológica integral

Síntese realizada pelo Dr. Manuel Salgado em relatório de consulta de Reumatologia a 06/03/1998

SÍNTESE:

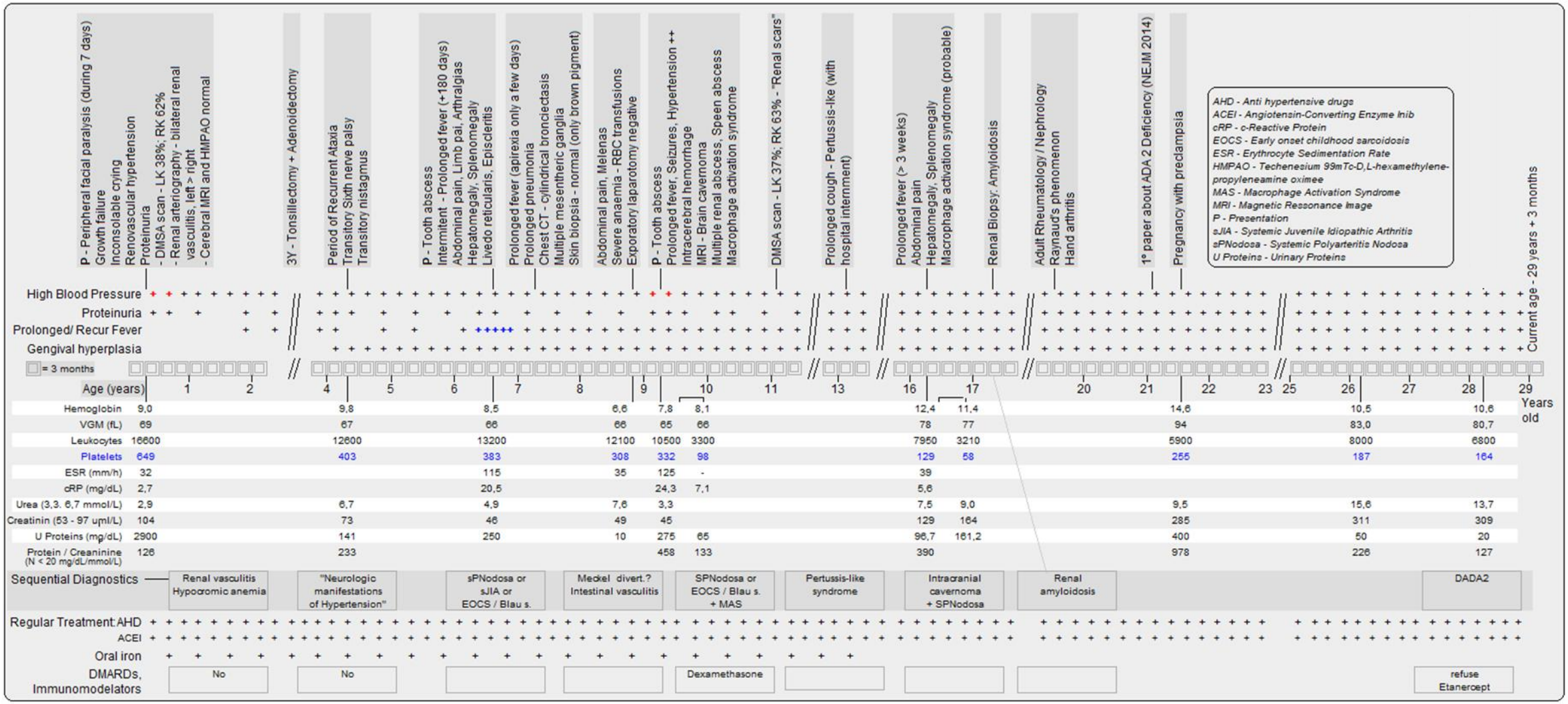
Na criança:

- HTA renovascular
- Estenose das artérias intrarenais
- Paralisia facial periférica
- Síndrome febril recorrente
- Síndrome febril prolongado
- Artralgias / Artrite
- Exantema intermitente
- Hepatoesplenomegalia
- **Livedo reticular** nas pernas
- Episclerite
- Dores abdominais recorrentes
- Hipocratismo digital (= pai)
- 4 internamentos em UCIP

Na mãe:

- Início semelhante
- Síndrome febril prolongado → AIJ sistémica
- **Livedo reticular** nas pernas
- Episclerite
- Uveíte
- Aftas bipolares → Doença Behçet

AVC hemorrágico
Episódio de hemorragia digestiva baixa
Biopsia renal – amiloidose secundária
Mãe falecida (mais tarde) de AVC aos 45 anos


P - Peripheral facial paralysis (during 7 days)
Growth failure
Inconsolable crying
Renovascular hypertension
Proteinuria
- DMSA scan - LK 38%; RK 62%
- Renal arteriography - bilateral renal vasculitis, left > right
- Cerebral MRI and HMPAO normal
3Y - Tonsillectomy + Adenoidectomy
Period of Recurrent Ataxia
Transitory Sixth nerve palsy
Transitory nistagmus
P - Tooth abscess
Intermitent - Prolonged fever (+180 days)
Abdominal pain, Limb pai, Arthralgias
Hepatomegaly, Splenomegaly
Livedo reticularis, Episcleritis
Prolonged fever (apirexia only a few days)
Prolonged pneumonia
Chest CT - cylindrical bronciectasis
Multiple mesentheric ganglia
Skin biopsia - normal (only brown pigment)
Abdominal pain, Melenas
Severe anaemia - RBC transfusions
Exporatory laparotomy negative
P - Tooth abscess
Prolonged fever, Seizures, Hypertension ++
Intracerebral hemorrhage
MRI - Brain cavernoma
Multiple renal abscess, Spleen abscess
Macrophage activation syndrome
DMSA scan - LK 37%; RK 63% - "Renal scars"
Prolonged cough - Pertussis-like (with hospital internment)
Prolonged fever (> 3 weeks)
Abdominal pain
Hepatomegaly, Splenomegaly
Macrophage activation syndrome (probable)
Renal Biopsy: Amyloidosis
Adult Rheumatology / Nephrology
Raynaud's phenomenon
Hand arthritis
1º paper about ADA 2 Deficiency (NEJM 2014)
Pregnancy with preclampsia
AHD - Anti hypertensive drugs
ACEI - Angiotensin-Converting Enzyme Inib
cRP - c-Reactive Protein
EOCS - Early onset childhood sarcoidosis
ESR - Erythrocyte Sedimentation Rate
HMPAO - Techenesium 99mTc-D,L-hexamethylene-propyleneamine oximee
MAS - Macrophage Activation Syndrome
MRI - Magnetic Ressonance Image
P - Presentation
sJIA - Systemic Juvenile Idiopathic Arthritis
sPNodosa - Systemic Polyarteritis Nodosa
U Proteins - Urinary Proteins
High Blood Pressure
Proteinuria
Prolonged/ Recur Fever
Gengival hyperplasia
Current age - 29 years + 3 months
= 3 months
Age (years)
1
2
4
5
6
7
8
9
10
11
13
16
17
20
21
22
23
25
26
27
28
29
Years old
Hemoglobin 9,0 9,8 8,5 6,6 7,8 8,1 12,4 11,4 14,6 10,5 10,6
VGM (fL) 69 67 66 66 65 66 78 77 94 83,0 80,7
Leukocytes 16600 12600 13200 12100 10500 3300 7950 3210 5900 8000 6800
Platelets 649 403 383 308 332 98 129 58 255 187 164
ESR (mm/h) 32 115 35 125 - 39
cRP (mg/dL) 2,7 20,5 24,3 7,1 5,6
Urea (3,3. 6,7 mmol/L) 2,9 6,7 4,9 7,6 3,3 7,5 9,0 9,5 15,6 13,7
Creatinin (53 - 97 uml/L) 104 73 46 49 45 129 164 285 311 309
U Proteins (mg/dL) 2900 141 250 10 275 65 96,7 161,2 400 50 20
Protein / Creaninine (N < 20 mg/dL/mmol/L) 126 233 458 133 390 978 226 127
Sequential Diagnostics
Renal vasculitis Hypocromic anemia
"Neurologic manifestations of Hypertension"
sPNodosa or sJIA or EOCS / Blau s.
Meckel divert.? Intestinal vasculitis
SPNodosa or EOCS / Blau s. + MAS
Pertussis-like syndrome
Intracranial cavernoma + SPNodosa
Renal amyloidosis
DADA2
Regular Treatment: AHD
ACEI
Oral iron
DMARDs, Immunomodelators
No
No
Dexamethasone
refuse Etanercept

EM 2014:

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mutant Adenosine Deaminase 2 in a Polyarteritis Nodosa Vasculopathy

Paulina Navon Elkan, M.D., Sarah B. Pierce, Ph.D., Reeval Segel, M.D., Tom Walsh, Ph.D., Judith Barash, M.D., Shai Padeh, M.D., Abraham Zlotogorski, M.D., Yackov Berkun, M.D., Joseph J. Press, M.D., Masha Mukamel, M.D., Isabel Voth, M.D., Philip J. Hashkes, M.D., Liora Harel, M.D., Vered Hoffer, M.D., Eduard Ling, M.D., Ph.D., Fatos Yalcinkaya, M.D., Ozgur Kasapcopur, M.D., Ming K. Lee, Ph.D., Rachel E. Klevit, D.Phil., Paul Renbaum, Ph.D., Ariella Weinberg-Shukron, B.Sc.Med., Elif F. Sener, Ph.D., Barbara Schormair, Ph.D., Sharon Zeligson, M.Sc., Dina Marek-Yagel, Ph.D., Tim M. Strom, M.D., Mordechai Shohat, M.D., Amihood Singer, M.D., Alan Rubinow, M.D., Elon Pras, M.D., Juliane Winkelmann, M.D., Mustafa Tekin, M.D., Yair Anikster, M.D., Ph.D., Mary-Claire King, Ph.D., and Ephrat Levy-Lahad, M.D.

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, S.J. Kelly, D.E. Kleiner, J.C. Mullikin, N.J. Ganson, H.H. Kong, S. Hambleton, F. Candotti, M.M. Quezado, K.R. Calvo, H. Alao, B.K. Barham, A. Jones, J.F. Meschia, B.B. Worrall, S.E. Kasner, S.S. Rich, R. Goldbach-Mansky, M. Abinun, E. Chalom, A.C. Gotte, M. Punaro, V. Pascual, J.W. Verbsky, T.R. Torgerson, N.G. Singer, T.R. Gershon, S. Ozen, O. Karadag, T.A. Fleisher, E.F. Remmers, S.M. Burgess, S.L. Moir, M. Gadina, R. Sood, M.S. Hershfield, M. Boehm, D.L. Kastner, and I. Aksentijevich

EM 2014:

Eur J Dermatol. 2003 May-Jun;13(3):283-7.

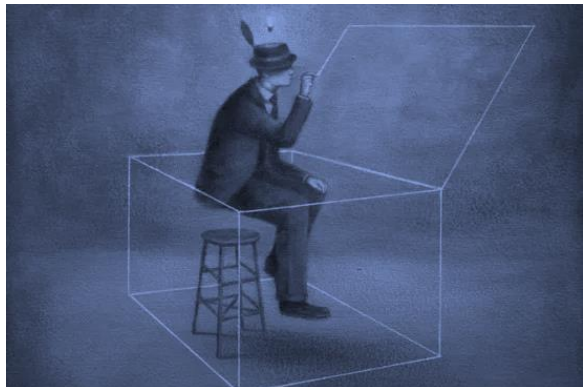
Familial Sneddon's syndrome.

Mascarenhas R[1], Santo G, Gonçalo M, Ferro MA, Tellechea O, Figueiredo A.

Author information

Abstract

A syndrome associating Livedo Reticularis (LR) with Cerebrovascular disease (CVD) was described, in 1965, by Sneddon. It occurs sporadically, but a few familial cases of Sneddon's Syndrome (SS) have been reported, like these 3 cases that represent one of the largest number among siblings. We studied three male brothers, aged 28, 37 and 42 years, with CVD (ischaemic stroke in 2 patients and cerebral haemorrhages in the third) and their sister with no CVD. All patients presented with long lasting Livedo Reticularis, extending beyond the lower limbs. Skin biopsy on the centre of the reticular pattern showed, only in the second patient, partial endothelium detachment in dermo-hypodermic blood vessels. The males also had accesses of Livedoid Vasculitis (LV), in which a skin biopsy showed obliteration of several upper dermal vessels with hialin thrombi and a very scarce inflammatory infiltrate. Complementary studies, with an extensive investigation on pro-coagulation/pro-thrombotic features including antiphospholipid antibodies, were repeatedly negative. Their non-consanguineous parents were not affected, but among these kindred of 9 individuals, apart from the 4 patients reported above, LR and LV were present in two other brothers and also in an aunt and uncle, suggesting autosomal dominant pattern of inheritance, with incomplete penetrance. The relationship between Sneddon's Syndrome and Antiphospholipid Antibody Syndrome is controversial. The present cases, having repeatedly negative antiphospholipid antibodies, support the classification of Sneddon's Syndrome as an independent nosological entity.

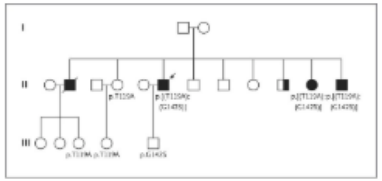


Pensar **Fora da Caixa** com
os **Pés Dentro da Caixa**

TO THE EDITOR

We identified a novel compound heterozygous mutation in CECR1 as the cause of Sneddon's syndrome in a Portuguese family. CECR1 mutations have recently been associated with a novel genetic condition, ADA2 deficiency, in children presenting with the first symptoms at early ages. The family, which has been described previously,[1,2] includes nine siblings. Livedo racemosa, leg ulcerations, and intermittent fevers that fluctuated with the seasons developed during the second decade of life in five siblings. Four of these siblings also had ischemic strokes, hemorrhagic strokes, or both during early adulthood (Figure 1).

Figure 1.



Pedigree of a Portuguese Family with Sneddon's Syndrome.

We performed exome sequencing in two siblings and identified a novel compound heterozygous mutation in CECR1: NM_177405; c.[355A→G];[424G→A], p.[(T119A);(G142S)]. We used Sanger sequencing to extend the analysis to other family members and confirmed the compound heterozygous status of the mutation and the complete segregation of mutation status and disease.

These findings expand the phenotype associated with mutations in CECR1 to include later onsets of disease, confirming that mutations in this gene may be more common than expected and may be associated with a larger spectrum of disorders.

Jose Bras, Ph.D.
Rita Guerreiro, Ph.D.
University College London Institute of Neurology, London, England
r.guerreiro@ucl.ac.uk

Gustavo C. Santo, M.D.
Coimbra's University Hospital, Coimbra, Portugal

ADA2 deficiency (DADA2) as an unrecognised cause of early onset polyarteritis nodosa and stroke: a multicentre national study

Roberta Caorsi,[1] Federica Penco,[1] Alice Grossi,[2] Antonella Insalaco,[3] Alessia Omenetti,[1,4] Maria Alessio,[5] Giovanni Conti,[6] Federico Marchetti,[7] Paolo Picco,[1] Alberto Tommasini,[8] Silvana Martino,[9] Clara Malattia,[1,4] Romina Gallizi,[10] Rosa Anna Podda,[11] Annalisa Salis,[12] Fernanda Falcini,[13] Francesca Schena,[1] Francesca Garbarino,[1,4] Alessia Morreale,[1,4] Manuela Pardeo,[3] Claudia Ventrici,[6] Chiara Passarelli,[14] Qing Zhou,[15] Mariasavina Severino,[16] Carlo Gandolfo,[16] Gianluca Damonte,[12] Alberto Martini,[1] Angelo Ravelli,[1,4] Ivona Aksentijevich,[15] Isabella Ceccherini,[2] Marco Gattorno[1]

ABSTRACT

Objectives To analyse the prevalence of *CECR1* mutations in patients diagnosed with early onset livedo reticularis and/or haemorrhagic/ischaemic strokes in the context of inflammation or polyarteritis nodosa (PAN). Forty-eight patients from 43 families were included in the study.

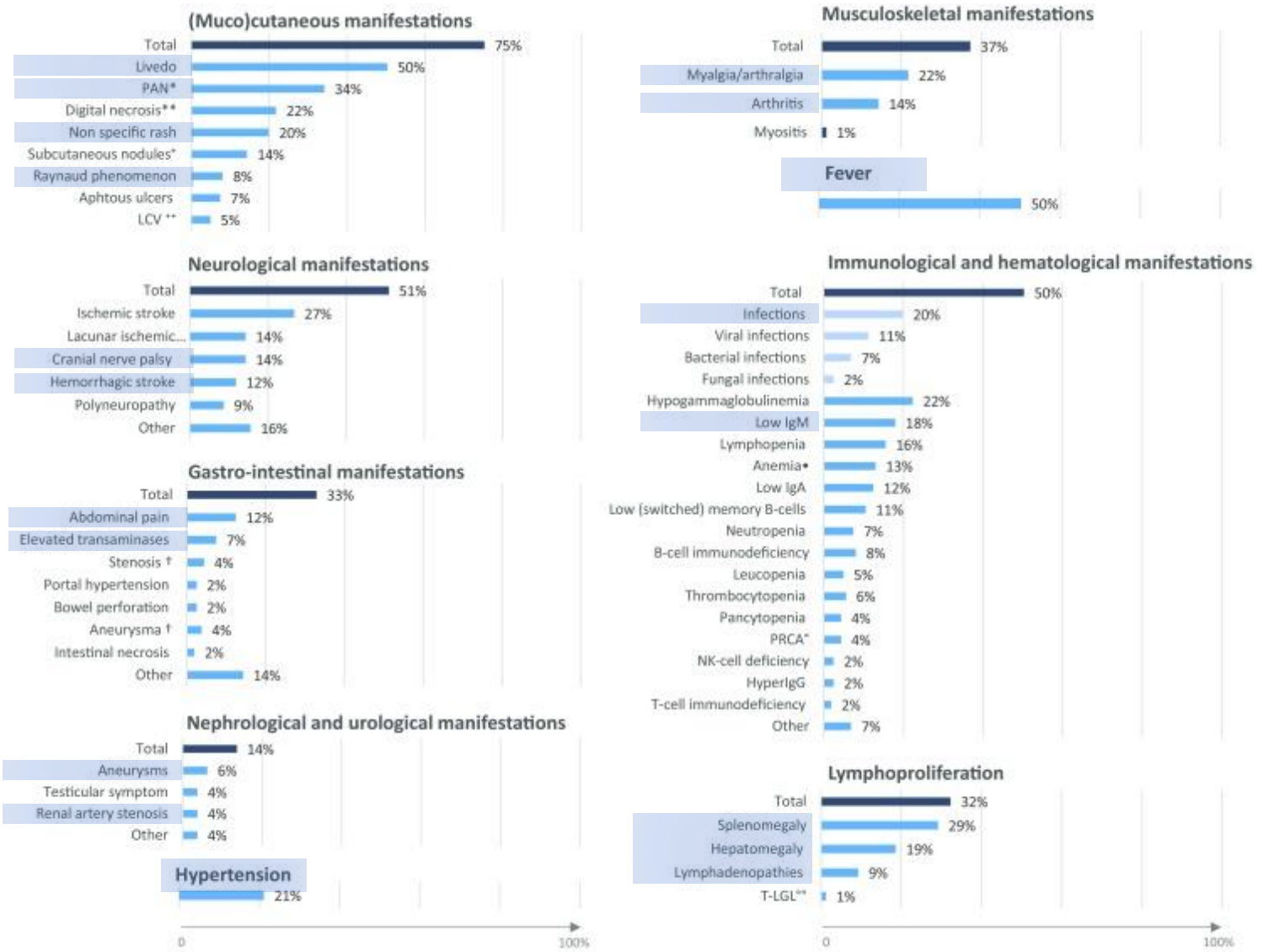
(Cat Eye Syndrome Chromosome Region 1) gene.[1 2] DADA2 is characterised by an early onset vasculopathy with clinical and histopathological features of polyarteritis nodosa (PAN), associated with haemorrhagic and ischaemic strokes.[1–3] Hypogammaglobulinaemia with reduction of memory and terminally differentiated B cells and

Fever of unknown origin with rashes in early infancy is indicative of adenosine deaminase type 2 deficiency

H Nihira, K Nakagawa, K Izawa, T Kawai, T Yasumi, R Nishikomori, M Nambu, A Miyagawa-Hayashino, T Nomura, K Kabashima, M Ito, S Iwaki-Egawa, Y Sasahara, M Nakayama & T Heike

Renal Amyloidosis in Deficiency of Adenosine Deaminase 2: Successful Experience With Canakinumab

Rabia Miray Kisla Ekinci, MD,[a] Sibel Balci, MD,[a] Atil Bisgin, MD,[b] Michael Hershfield, MD,[c] Bahriye Atmis, MD,[d] Dilek Dogruel, MD,[e] Mustafa Yilmaz, MD[a]



*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;

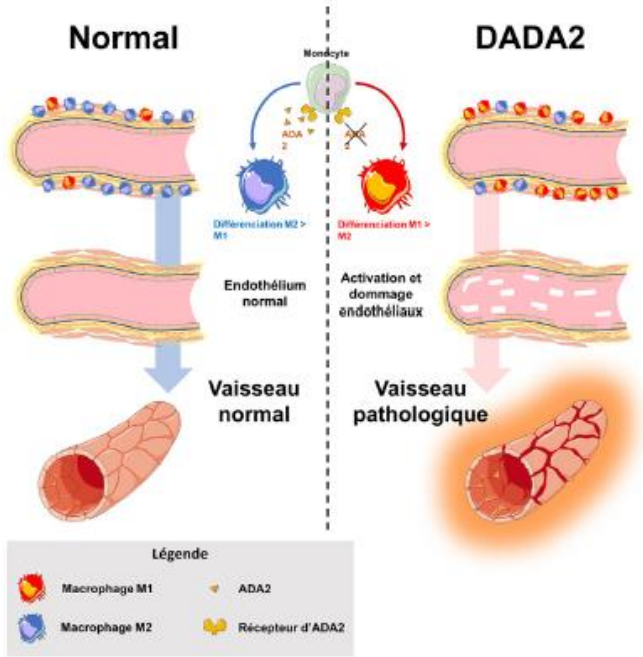
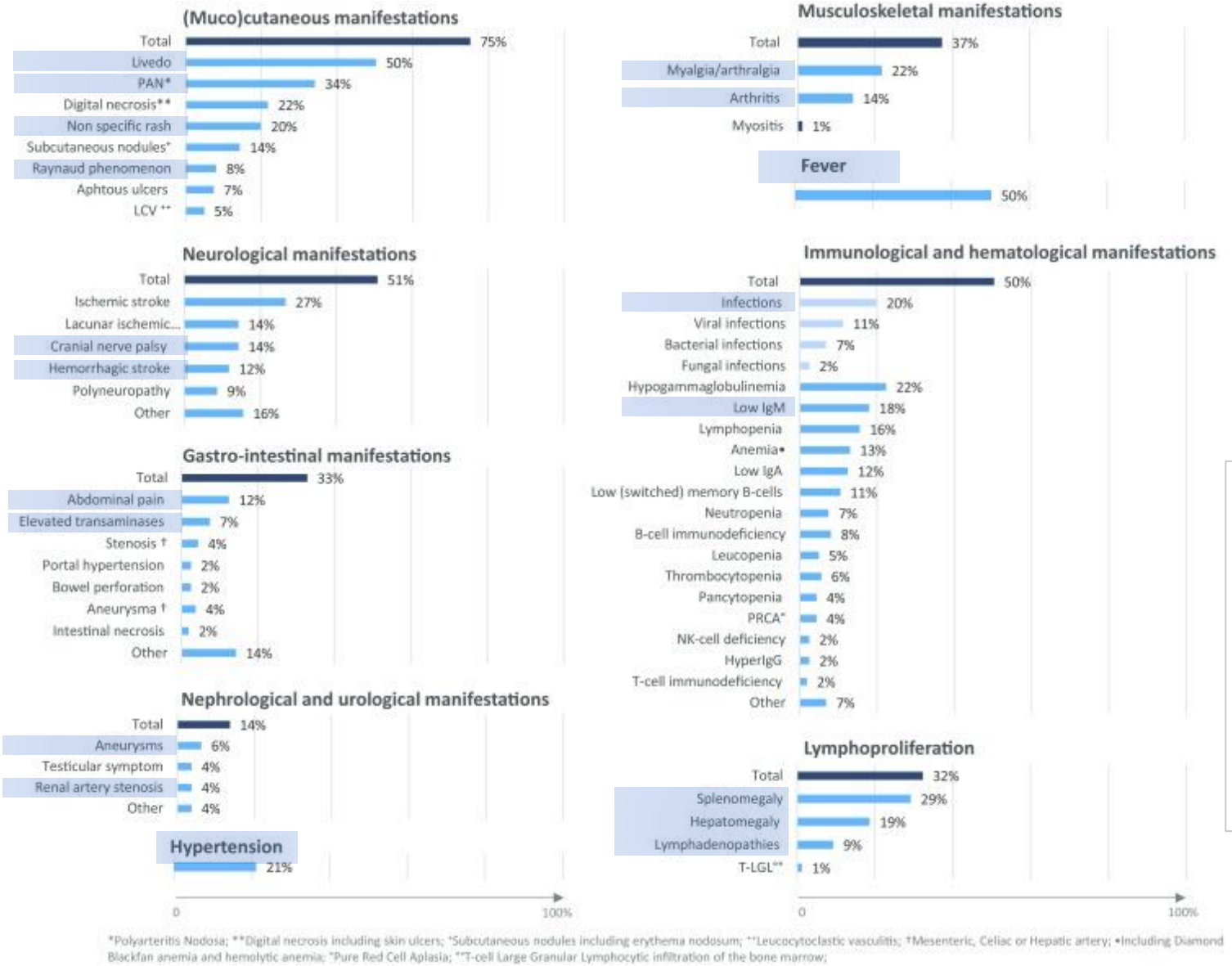
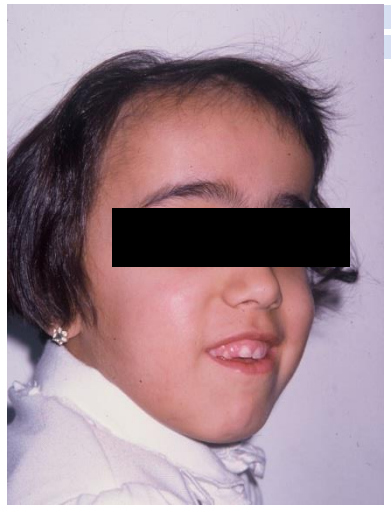


Fig. 5. Physiopathologie du DADA2. En situation physiologique l'ADA2 agit comme facteur de croissance monocytaire et promeut la différenciation en macrophage M2 plutôt que M1. En l'absence d'ADA2 la différentiation se fait préférentiellement vers un phénotype M1 pro-inflammatoire. On suppose que l'ADA2 a une activité facteur de croissance semblable sur la cellule endothéliale : ainsi, en son absence on observe une activation endothéliale à l'origine de dommages vasculaires. Ces deux mécanismes associés aboutissent aux manifestations vasculaires et/ou inflammatoires du DADA2 telles que le livedo, la fièvre récurrente ou les accidents vasculaires cérébraux.

Myets I et al. J Clin Immunol. 2018;38(5):569-578





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).

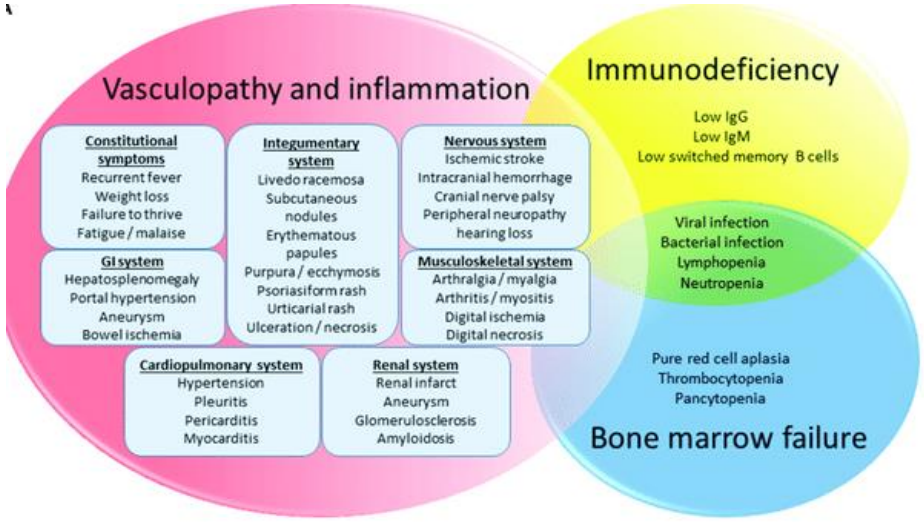
Data: 20/3/2019

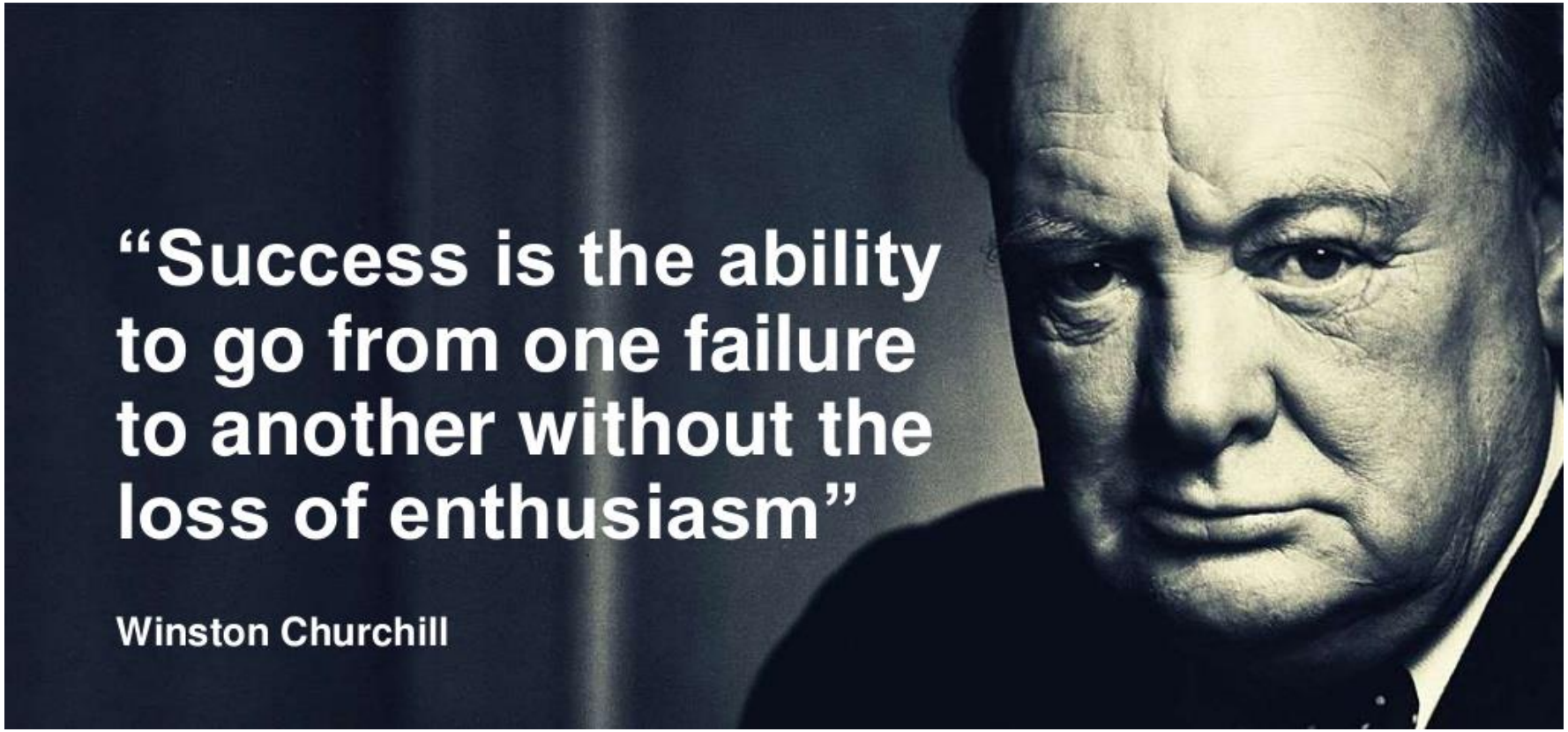
Mutação em homozigotia Tyr453Cys

COMENTÁRIOS

- A deficiência de adenosina deaminase 2 (DADA2) é um síndrome autoinflamatório monogénico que se carateriza por vasculopatia de início precoce, inflamação sistémica, envolvimento multiorgânico e imunodeficiência
- A presença de **história familiar** sugestiva em pacientes com ***livedo*** e **fenómenos trombóticos** deve levantar a suspeição desta patologia
- O diagnóstico e intervenção terapêutica precoces podem melhorar de forma significativa o prognóstico e possivelmente evitar futuras complicações

Este caso de diagnóstico tardio oferece-nos uma janela imperdível para a **história natural** da doença e para a **variabilidade fenotípica** do seu espetro





Obrigado pela atenção