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Management of DBA in adults

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ERN-EuroBloodNet

Paris, France

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APLASIE MEDULLAIRE centre de référence

MaRIH Filière de santé Maladies Rares Immuno-Hématologiques

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Conflicts of interest

No conflict of interest

Learning objectives of the webinar

1. To think about DBA in adults and to know how to diagnose it

2. To know how to treat DBA in adult patients

3. To know how to follow adult patients with DBA

DBA in brief

Rare disease (5 to 7/1,000,000 live births in EU)

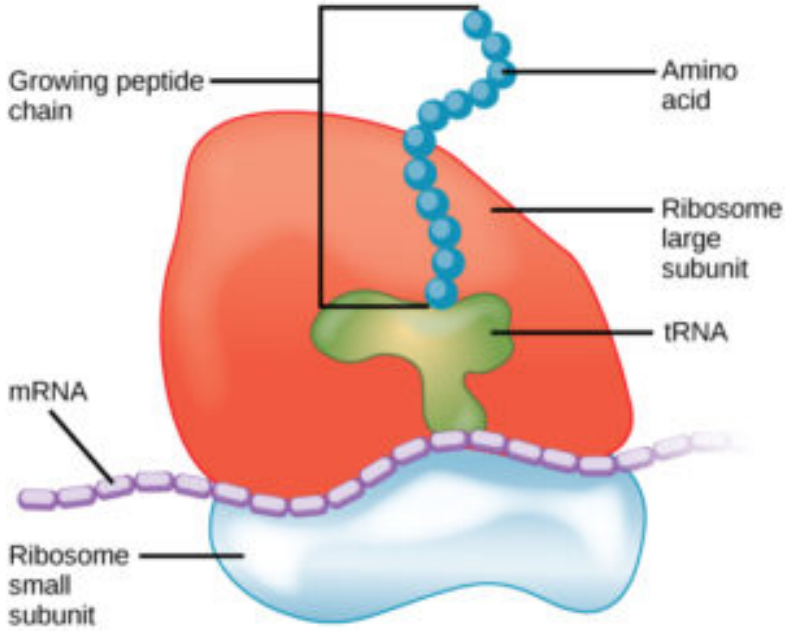
Main cause of constitutional erythroblastopenia

Ribosomopathy

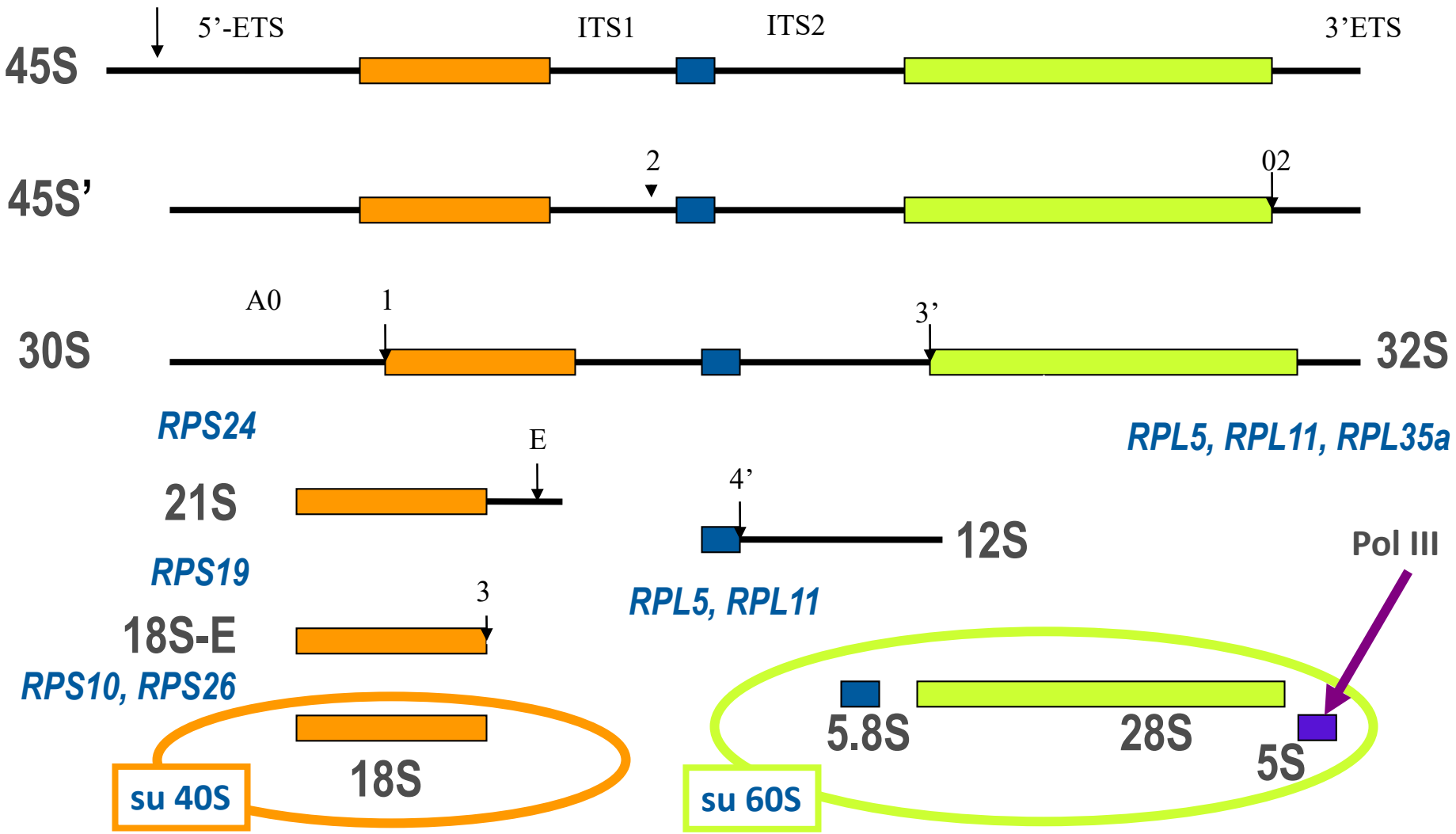
Genetic transmission: mostly AD but not so simple:

- *Problem of «silent career»*
- *AR & X-linked transmission also reported*

Very heterogeneous disease both for genetic & for clinical aspects



Ribosomopathy



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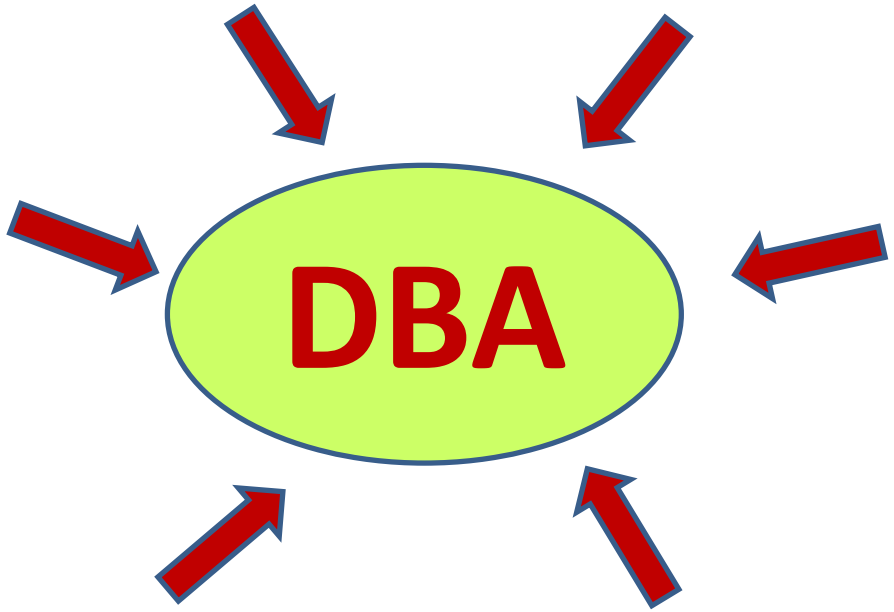
DBA in adults: clinical presentations

Severe or mild anemia (macrocytosis, low reticulocytes)

Hypoγglobulinemia & CVD

Asymptomatic pts
- parent of affected-child
- donor screening for BMT



Complicated pregnancies

MDS-like features
&
« true » MDS

Solid tumors, unexpected toxicity of chemotherapy

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CASE REPORT

Adult-onset Diamond-Blackfan anemia with a novel mutation in the exon 5 of RPL11: too late and too rare

Elena Flores Ballester[1], Juan José Gil-Fernández[1], Miguel Vázquez Blanco[2], José M. Mesa[3], Juan de Dios García[3], Ana T. Tamayo[1] & Carmen Burgaleta[1]

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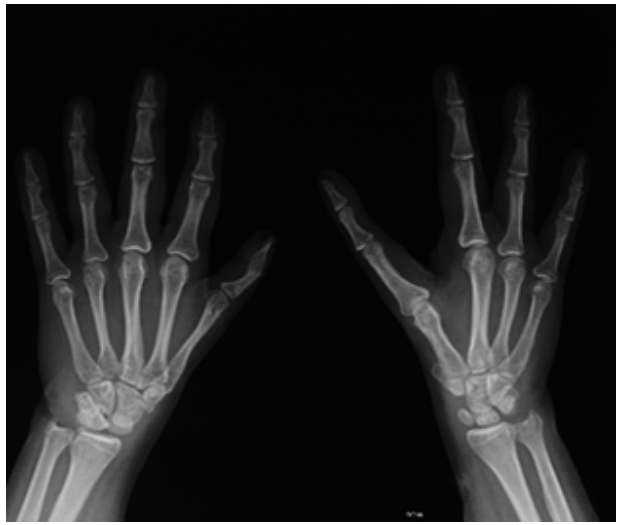
Age at diagnosis: 35 yr

Hb: 7.2 g/dL, MCV 93 Rt: 13 G/L

GB: 4.3 G/L

Platelets: 342 G/L



No previous BCC available

Exemples of BCC in DBA pts (not transfused)

Date	Hb (g/dL)	MCV (fl)	RT (G/L)	Neutrophils (G/L)	Platelets (G/L)
30/09/2009	11.5	106	60	1.70	331
21/11/2012	10.6	103.9	45.7	2.57	265
27/11/2013	10.4	10.,3	22.2	1.64	296
21/05/2014	11.2	107.6	55.3	1.48	288
03/06/2015	9.2	101.2	6.9	1.14	289
02/12/2015	10.8	105	66.8	1.19	309
01/06/2016	10.6	105.8	42.6	2.27	ND
19/08/2016	11.5	105	51.2	1.17	321
29/11/2016	10.3	105	44.8	1.52	286
14/12/2016	10.7	103.8	ND	2.11	285
09/06/2017	11.6	106	66.57	1.66	278
22/11/2018	11.4	104	73.4	1.00	298
20/02/2019	10,8	105,9	46,4	1,28	322
25/07/2019	11.4	107	ND	1.19	333
20/02/2021	11.3	105	73.1	1.25	311

Woman born in 1965; therapeutic independence

Date	Hb (g/dL)	MCV (fl)	RT (G/L)	Neutrophils (G/L)	Platelets (G/L)
16/06/2014	13.7	96	41.	3,875	219
15/10/2014	14	97.5	46.	6,300	251
01/12/2014	13.6	120	45.1	4,620	251
18/04/2015	13.	99	40.00	3,574	213
24/06/2015	14.	97.1	46.10	3,770	209
02/04/2016	14.6	97	48.51	7,228	279
09/11/2016	14.9	96.4	39.6	5,230	230
12/07/2017	12.8	100	ND	7,605	262
25/10/2017	13.4	95.2	67.2	8,720	277
02/07/2018	11.7	101	14	4.221	236
13/10/2018	13	99	80	3.55	242
13/03/2019	13.9	94.2	56.5	7.53	279
05/07/2019	13.2	98	51.5	7.80	237
23/11/2019	13	96.3	55.2	7.43	250
23/05/2020	13.4	95.4	69.9	7.94	253
26/09/2020	13.1	95.2	69.3	7.33	242
24/03/2021	13.6	96.6	60.6	7.90	297

Man born in 1966; on prednisone 10mg/d

(response obtained post metoclopramide trial. Abkowitz & al, Blood 2002)

How to confirm DBA?

1. Fetal hemoglobin: good screening test

2. eADA: erythrocyte deaminase (before any transfusion)

3. rRNA analysis

4. Hypo-Ig G, A, M (DBA & DADA2 syndrome)

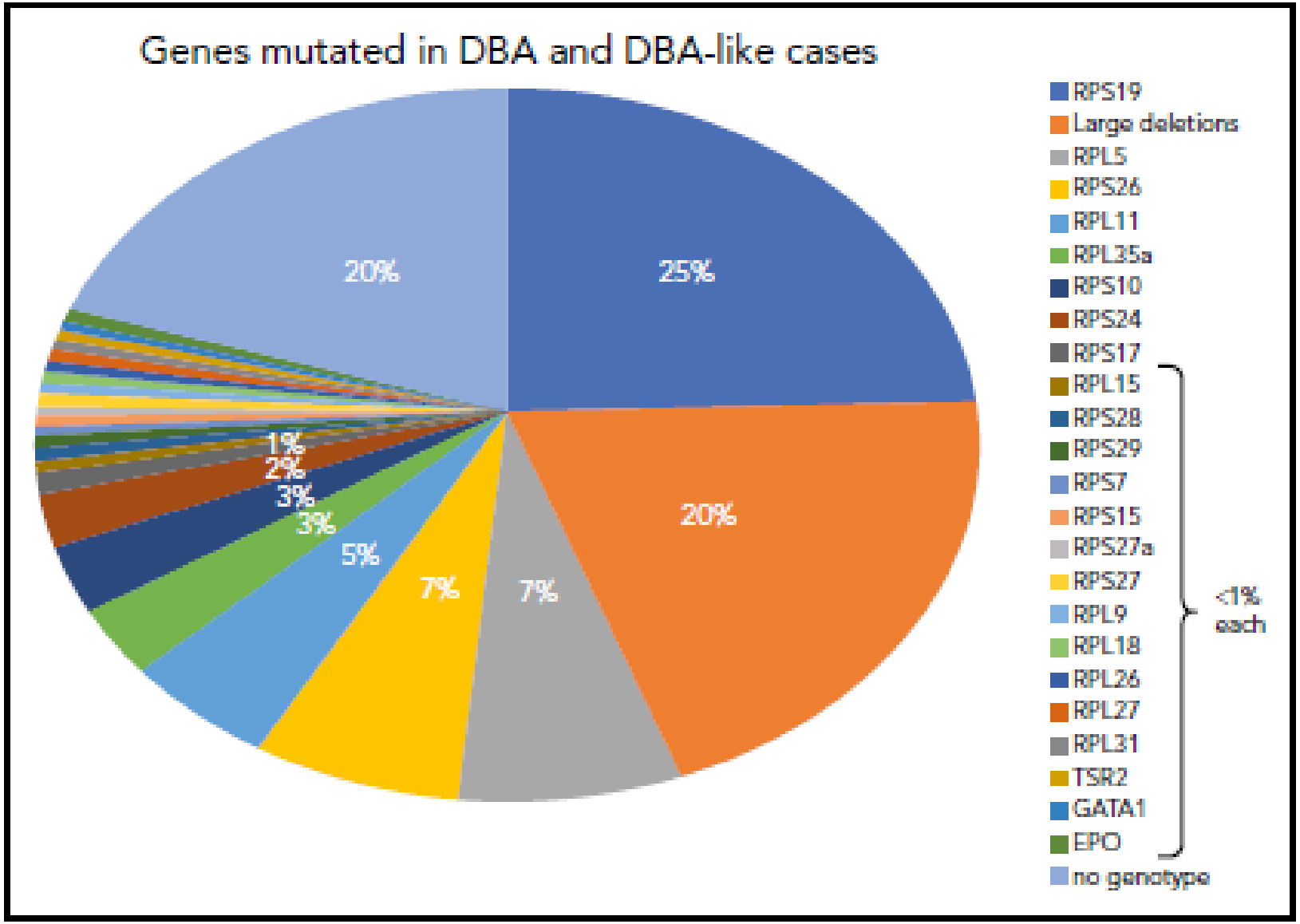
5. Bone marrow aspiration analysis + Perls coloration:
   - *Erythroblastopenia or reduced erythrocyte lineage*
   - *No dysplasia (if YES: cytogenetics analysis)*
   - *No sideroblasts*
   - *BM overall rich & normal for other lineages*

Bone marrow biopsy?

6. Genetic tests

DBA Genetics (1)

Mutated gene	RP	Incidence in DBA population	Reference
Genes involved in DBA*			
RPS19	eS19	25%-30%	7,51,53-55,102
Large deletions		10%-20%	60,66-69
RPL5	uL18	7%-12%	7,57-59
RPS26	eS26	6.6%-9%	7,64
RPL11	uL5	5%-7%	7,57-59
RPL35a	eL33	2%-3%	7,60
RPS10	eS10	1%-3%	7,64
RPS24	eS24	2.4%-3%	7,61
RPS17	eS17	1%-3%	7,62,63
RPL15	eL15	1 case 6 cases	12,73
RPS28	eS28	2 families	48
RPS29	uS14	2 families	71
RPS7	eS7	1 case	58
RPS15	uS19	1 case	58
RPS27a	eS31	1 case	58
RPS27	eS27	1 case	70
RPL9	uL6	1 case	58
RPL18	eL18	1 family	71
RPL26	uL24	1 case	74
RPL27	eL27	1 case	70
RPL31	eL31	1 case	75
TSR2 (X linked)†		1 family	48
Genes involved in DBA-like diseases			
GATA1 (X linked)‡		5 families	47,77-80
EPO		1 case	46
ADA2§		9 individuals	7



(Da Costa L, Leblanc T, N Mohandas, Blood 2020)

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DBA Genetics (2)

☞80% patients: identified mutation (NGS+CGH-array):

- 20 RP genes (+++ *RPS19*); AD transmission
- 1 non RP gene but product implicated in ribosome biogenesis: *TSR2*: X-linked transmission

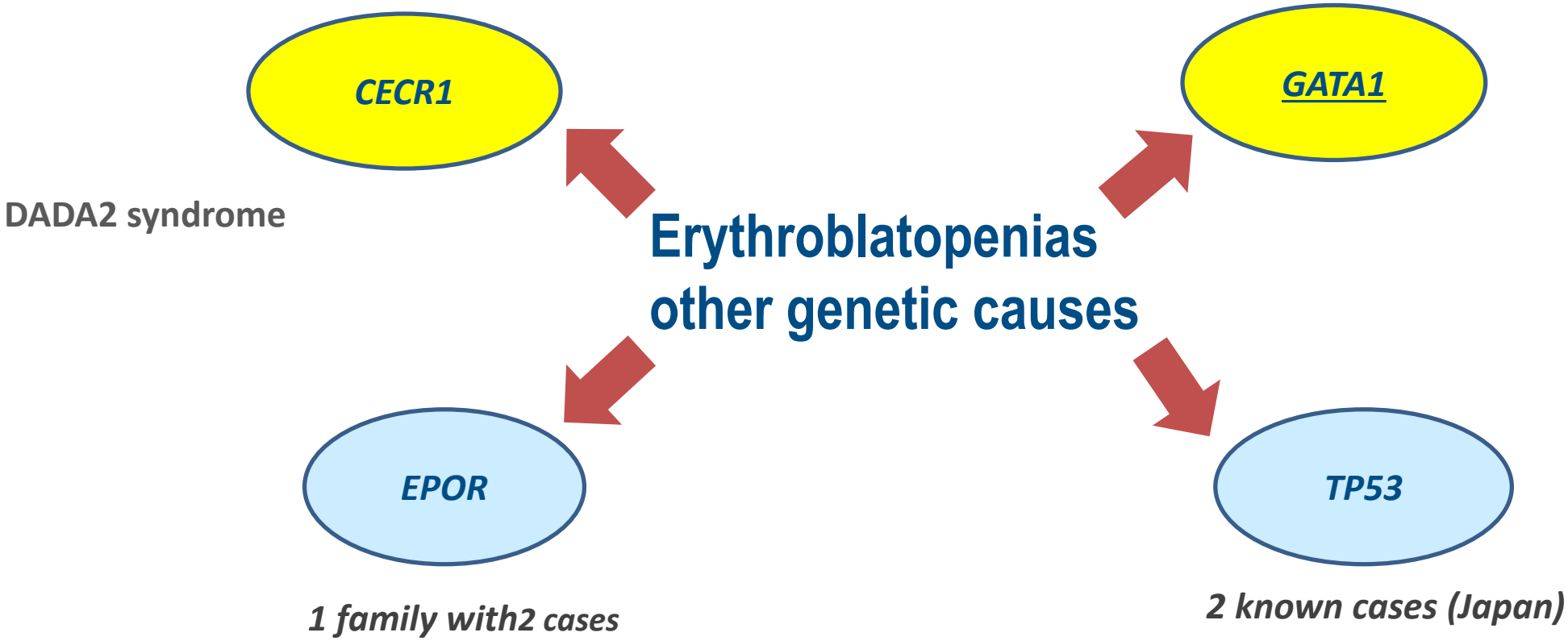
+ genes associated with other constitutional erythroblastopenias: *GATA1* (X), genes *CECR1/ADA2* (AR) & *EPO* (AR)

NB1: RPS19, RPL5, RPLL11, RPS26, RPL35A, RPS17: 96% of mutations

NB2: large deletions frequent for RPS17, RPS19, RPS26 RPL5, RPL11, RPLL35a,

☞20% patients: no identified mutation ☞ exome

Other Constitutional erythroblastopenias: DBA syndrome



How to treat adult DBA patient with anemia ?

1. Transfusions: recommended threshold: 90 to 100 g/dL

- Usually 2 to 3 red cells unit every 3 to 4 weeks
- Take into account QOL
- Less intensive in pts with “high” levels of reticulocytes

NB: about 20% of pts are free of any treatment

2. Glucocorticoids:

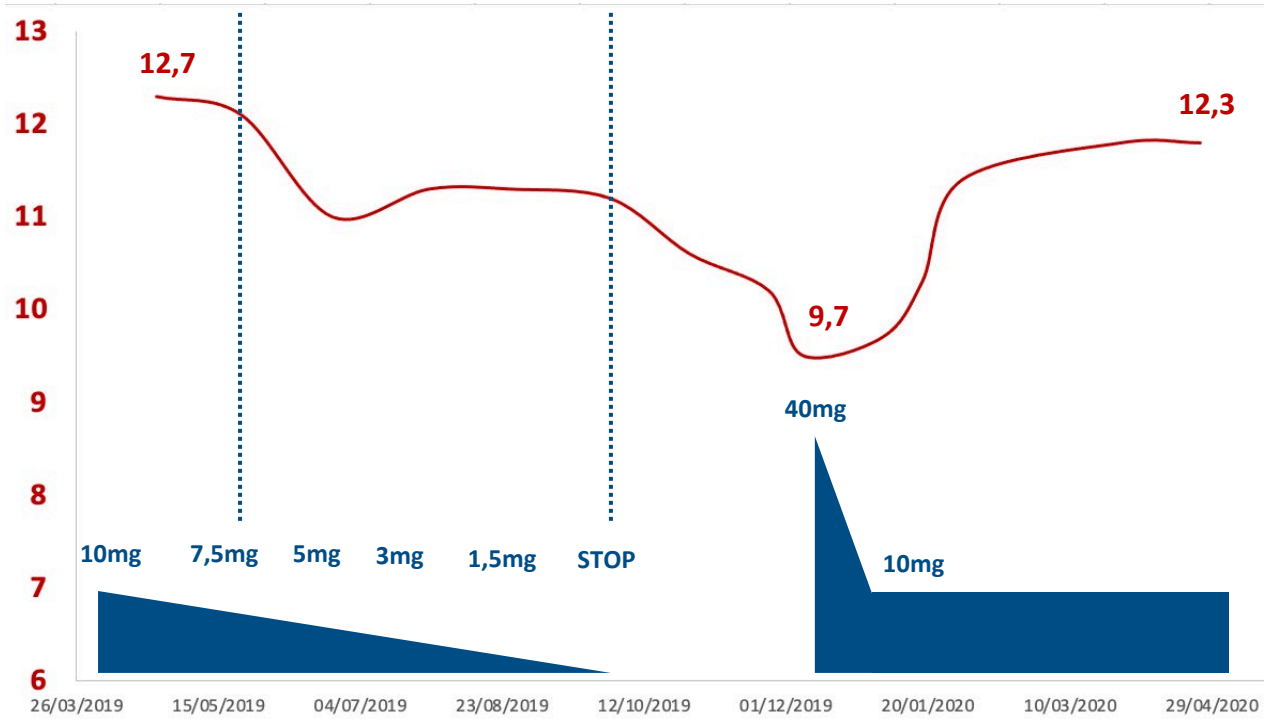
- Start prednisone at 2 mg/kg/d (maximal dose 80 mg/j)
- Taper as soon as reticulocytes rise is present (D10)
- Define the minimal efficacious dose

  NB: in adult maximal tolerable dose: 10 mg/day

Mother of a child with DBA; identified mutation in both.
Classified as «silent career».
Cancer: unexpected need for transfusion during treatment & after.
Test for predisone efficacy after OK from the oncologist.

Hb level

Prednisone



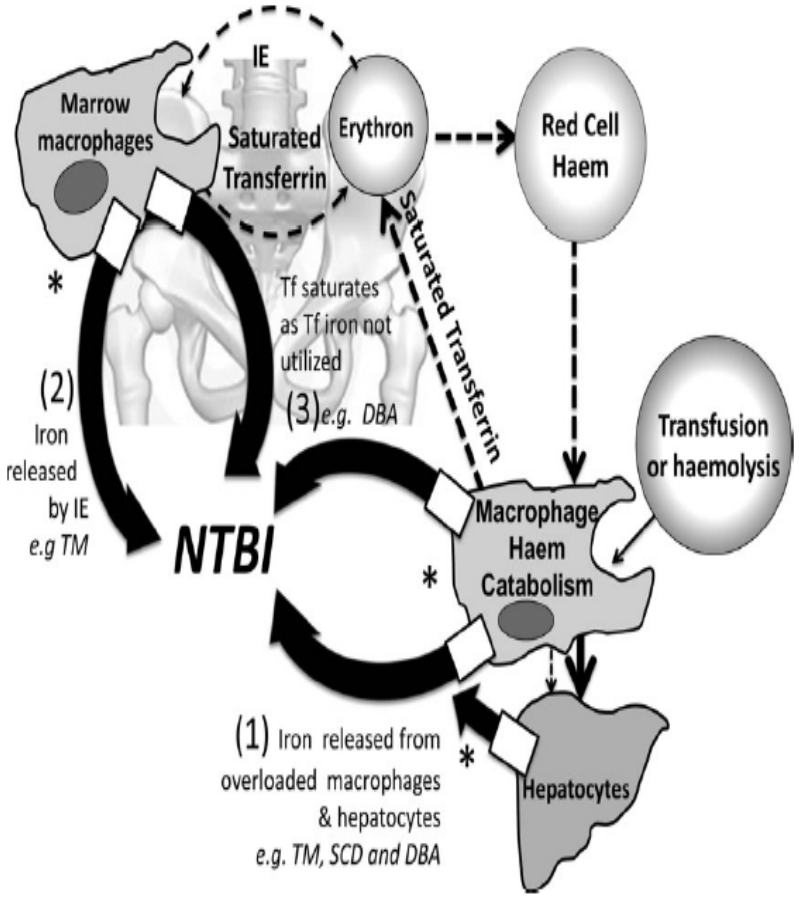
DBA treament in adults

Transfused patients:

Very quick iron loading

Chelation therapy +++

- ☞ combination of two chelators frequently required
- ☞ High risk of agranulocytosis with deferiprone (~ 10%)



(Porter & al, Br J Haematol 2014)

Patients on steroids:

Unique disease for the duration of steroid treatment!

Prevention of steroid-associated toxicity +++

Loss of steroid-response not rare with aging: in some pts the choice will be between "too much steroids" (e.g. 15 or 20 mg/d) and transfusions…

DBA: alternative therapeutic approaches?

1. Leucine:

- Very few data in adult patients
- May improve general status?
- May improve response to steroids allowing dose reduction?
- Published dose: 700 mg/m² x 3/d

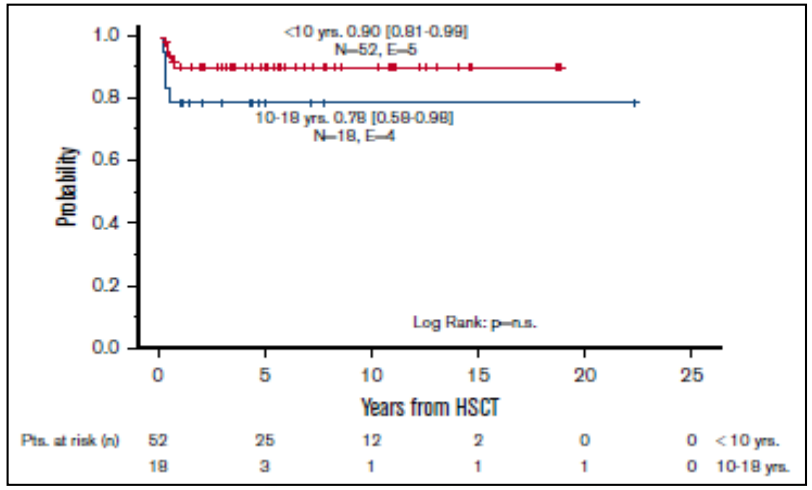
2. Metoclopramide *(Abkowitz & al, Blood 2002, Leblanc & al, Blood 2006)*

3. Bone marrow transplantation?

- Likely to be too toxic in adult patients
- Only indication: clonal evolution if the pt is fit enough

4. Gene therapy: for DBA pts mutated in *RPS19* in the future

Item and specification	n	OS Prob.	OS 95% CI	OS P
Number of patients	70	91	84-98	
Year of HSCT				
<2000	19	79	60-98	
≥2000	51	96	90-100	.03
Sex				
Male	44	95	89-100	
Female	26	84	69-99	.08
Age at HSCT, y				
<10	52	94	87-100	
10-18	18	82	63-100	NS
<5	34	97	91-100	
5-9	18	88	72-100	
10-14	13	85	65-100	
15-18	5	75	32-100	NS



(Strahm & al, Blood advances 2021)

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DBA: clinical outcomes in adult patients: hematology

More severe anemia:

- Need for higher transfusion support in transfused pts
- Loss of response to steroids

Leuconeutropenia: frequent but not clinically relevant

Overall bone marrow failure?

MDS & AML:

- Very high risk in DBA patients: O/E ratio claimed to be as high as 287

(Vlachos & al, Blood 2012)

- Difficult diagnosis! Must relies mostly on cytogenetics & molecular analysis

Current recommendations:

- BCC + reticulocytes every 3 months

Warning events: thrombocytopenia, paradoxal rise in reticulocytes

- Sequential bone marrow aspiration?

No clinical benefit demonstrated so far

To be considered in DBA pts fit enough for HSCT?

Incidence of neoplasia in Diamond Blackfan anemia: a report from the Diamond Blackfan Anemia Registry

Adrianna Vlachos,[1-3] Philip S. Rosenberg,[4] Eva Atsidaftos,[1,2] Blanche P. Alter,[5] and Jeffrey M. Lipton[1-3]

US registry study

N = 608

FU: 9458 person-years

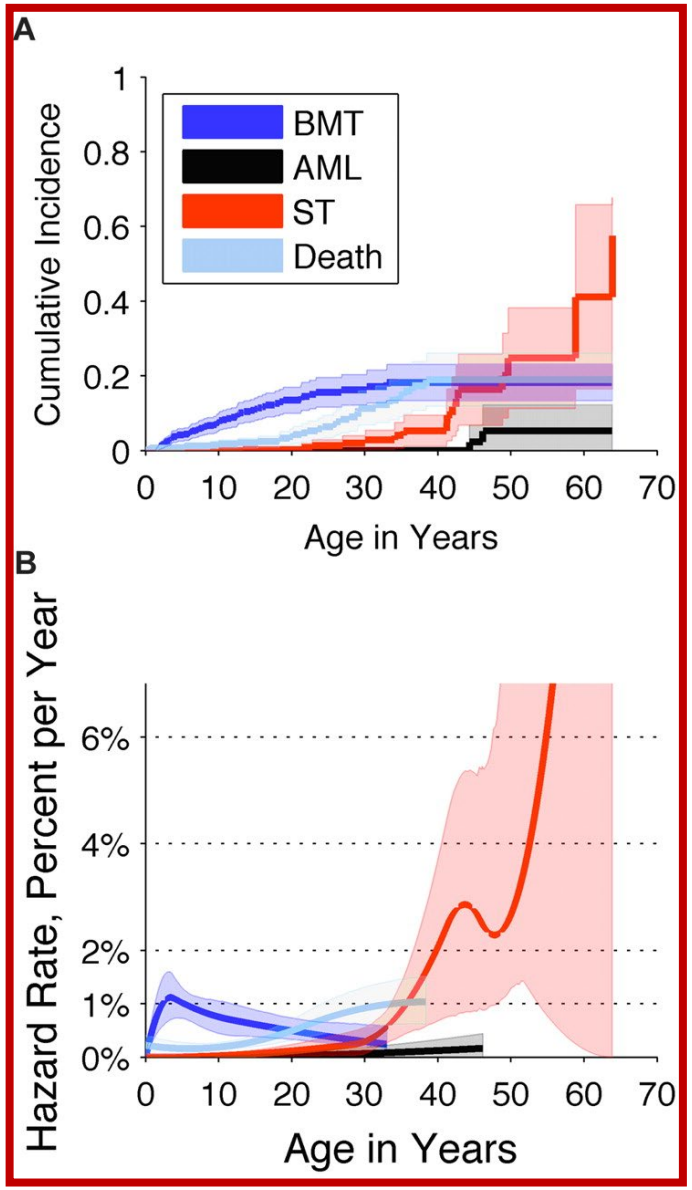
Solid tumors	*: 15*
AML	*: 2*
MDS	*: 2*

(Blood 2012)

Median age: 41 yr

Cumulative incidence (MDS/AML+ST) at 46 yr: 20%

To note: various ST types



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Cancer type	No. of observed cancers	O/E Ratio	95% CI
Events with significant O/E ratios			
All cancers	18	5.4	3.2 - 8.6
Colon (adenocarcinoma)	3	36.2	7.5 - 105.8
Bones (osteogenic)	2	32.6	4.0 - 117.7
Female genital	3	12.0	2.5 - 35.1
AML	2	27.9	3.4 - 100.9
MDS	4	287.0	77.2 - 734.7
Events with non significant O/E ratios			
Oral cavity	1	15.9	0.4 - 88.3
Soft tissue sarcoma	1	9.8	0.3 - 54.8
Lung	1	8.3	0.2 - 46.4
Testis	1	8.3	0.2 - 46.1
Non-Hodgkin lymphoma	1	5.7	0.1 - 31.7
Melanoma	1	4.5	0.1 - 25.3
Breast	2	4.1	0.5 - 14.9

DBA: clinical outcomes in adult patients: solid tumors

Increased risk of colon cancer and osteogenic sarcoma in DBA running head: neoplasia in DBA

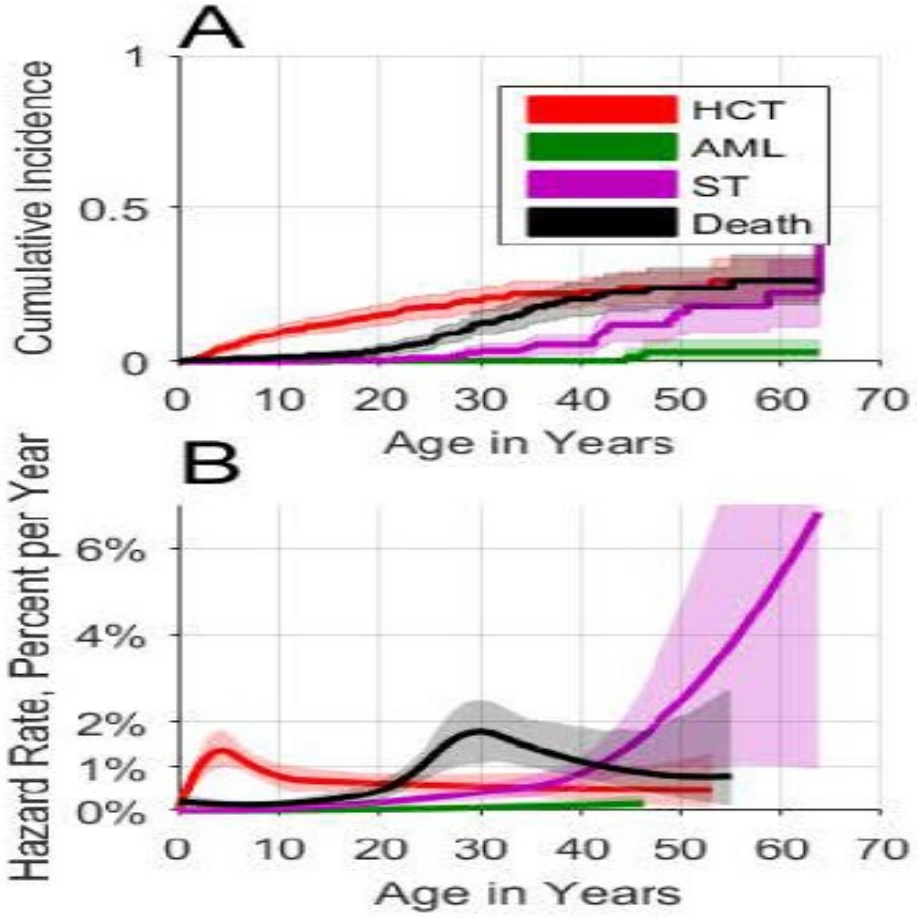
DBAR: 2nd report (N = 702)

+ 94 pts & +2198 pts/yr FU duration

34 cancers (in non grafted pts)

Median age at 1st cancer: 35 yr [11-70]

Cumulative incidence at 45 yr: 13,7%



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(Vlachos & al, Blood 2018)

Oncolology: FU of adult DBA patients

Do we have to screen for cancer in DBA patients?

Problem: many different solid tumors

At least:

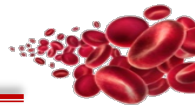
1) Clinical information for patients, family support groups, and physicians

2) Recommendations to strictly follow suggested measures for the general population

3) Additional screening?

Most discussed at the moment: coloscopy: every 5 years from the age of 25?

DBA: clinical outcomes in adult patients: immunology



1) Risk for hypo-γ-globulinemia: CVD profile

NB: *CECR1 mutations*: early event: DADA2 syndrome

- Very few clinical problems in my adult patients but…
- Associated with monoclonal proteins?

2) Lymphopenia:

- May be severe
- In pts on steroids or not

Immunolology: FU of adult DBA patients

Yearly immunologic evaluation: +++ Ig G, A, M levels

In a patient with low Ig levels:

☞ consider specific immunizations: pneumococcal & meningococcal vaccination

☞ Lung scan

☞ Ig supplementation if clinical infections or occult lung disease

Date	IgG (g/L)	IgA (g/L)	IgM (g/L)	CD3 /mm³	CD3/4 /mm³	CD3/8 /mm³
2.11.2019	2.32	0.28	0.49	NA	NA	NA
23.09.2020	2.39	0.28	0.49	488	191	271
24.03.2021	1.75	0.23	0.74	494	181	293

DBA pt born in 1966; on prednisone: 10 mg/day
Vaccinations & cotrimoxazole prophylaxis

DBA patients on transfusion FU (1)

Efficacy of transfusion support:

QOL analysis

Higher requirement with age

Iron loading FU:

Ferritin levels & transferrin saturation:
Before each transfusion?

MRI evaluation: liver & heart: every 12 to 24m

Hemochromatosis:

Regular checks for diabetes, hypopara-thyroidy, hypothyroidy, hypognoadism, liver functions, cardiac function,…

Follow up for chelators toxicity

DBA patients on transfusion FU (2)

Goals for iron loading control:

- Normal liver MRI
- Low levels of ferritin: 500 to 700 µg/L & and at best 300 to 500 µg/l

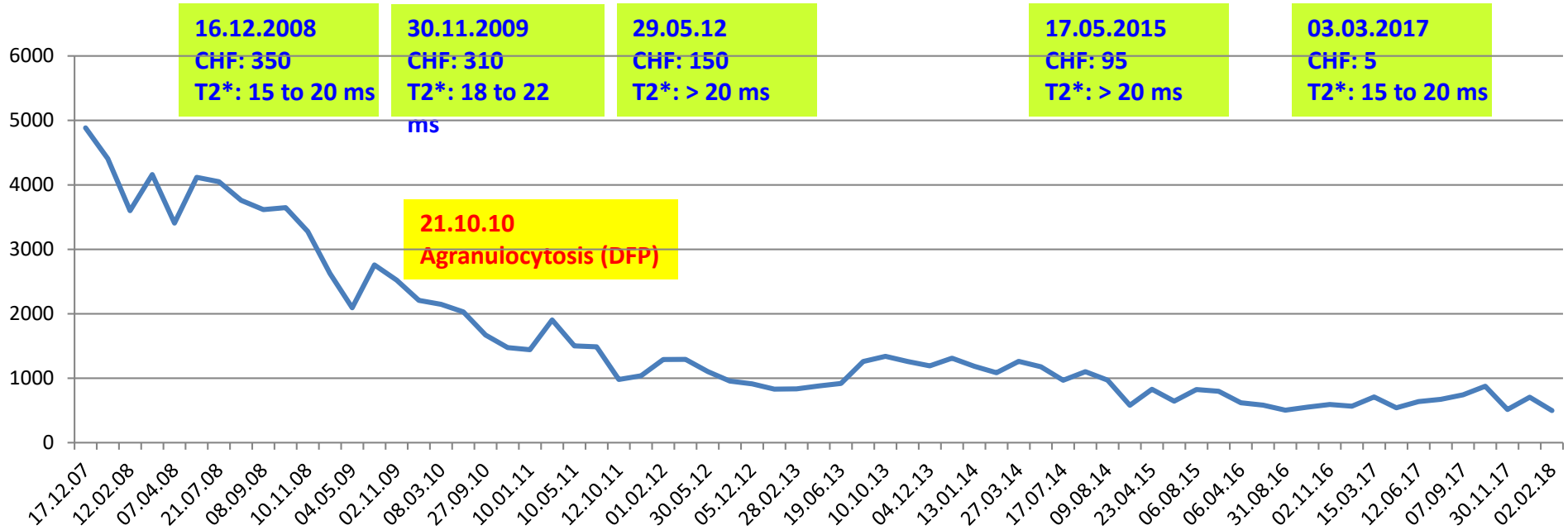
To note:

1) even in pts with very good control, the transferrin saturation remains in the 80 to 100% range ☞ toxicity of NTBI still present. The best is to give a chelator ANY day

2) Be aware of **hyperchelation**: toxicity of chelators is more important when ferritin is low

Ex. for deferasirox: risk for tubulopathy (hypophosphoremia) and urinary lithiasis

Woman, born in 79. DBA. Past history: hepatitis C. On transfusions: 2 units every 3 weeks then 3 units/ month. 1st visit (25.10.05): ferritin: 5014µg/L (chélation stopped for years); clinical hemochromatosis: hypothyroïdy, diabetes & hypogonadism



Chélation changes according to efficacy, chelator toxicity & patient adhesion):

CHF: µg of iron/g of liver

25.05.07	D1 DFX 1500mg/d	27.03.13	DFX 1000 mg/d
29.08.07	DFX 2000mg	08.01.14	DFX 500mg x 2/d x 4 days a week
08.12.08	DFX 2125 mg	14.05.14	DFX same dose for 5 days
02.07.10	DFO + DFP	13.05.15	DFX a 625 mg x 2 for 5 days
06.10.07	DFP dose correction	16.09.15	DFO 3 d a week + DFX for 5d 750 mg x 2
21.10.10	Agranulocytosis	14.02.18	DF0+DFX new formulation: 360mg x2/d
08.06.11	DFO + DFX 1500 mg/d x 2d/w		

DBA patients on prednisone FU

Efficacy

Prednisone may be less active with aging

Discussion with the patient on the benefice/risk ratio for steroids and transfusions

Check for steroid toxicity

Mostly:

Metabolic syndrome

Oteoporosis:

- Prevention with vitamin D
- Sequential osteodensitometry evaluations
- Biphosphonates may be needed in selected pts

DBA: clinical outcomes in adult patients: pregnancies

N = 64 pregnancies

Disorders of Erythropoiesis • Brief Report

High-risk pregnancies in Diamond-Blackfan anemia: a survey of 64 pregnancies from the French and German registries

Laurence Faivre
Jörg Meerpohl
Lydie Da Costa
Isabelle Marie
Christian Nouvel
Astrid Gnekow
Christine Bender-Götze
Francis Bauters
Bertand Coiffier
Pierre-Yves Peaud
Patrick Rispal
Alain Berrebi
Claire Berger
Michel Flesch
Paul Sagot
Bruno Varet
Charlotte Niemeyer
Gil Tchernia
Thierry Leblanc

We reviewed 64 pregnancies in 26 women with Diamond-Blackfan anemia (DBA) included in the French and German DBA registries. Complications were seen in 42 pregnancies (66%) and included abortion, pre-eclampsia, *in utero* fetal death, intrauterine growth retardation, retroplacental hematoma, pre-term delivery and fetal malformations. Of the 34 children (53%) born alive, 13 had DBA. No correlations were found between pregnancy outcome and features of either maternal or child DBA. Pregnancies in DBA-affected women are at high risk, especially for complications likely to be of vascular-placental origin. Careful monitoring with prevention of severe anemia and early introduction of aspirin is suggested.

Key words: Diamond-Blackfan anemia, pregnancies, vascular placental complications.

Haematologica 2006; 91:530-533

Main points:

- Iron loading control before pregnancy
- High level of care maternity (Grade III)
- Hb to be maintained > 10,5 g/dL
- Aspirin use to be discussed

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DBA: genetic counseling

Difficult task in DBA

Main points:

1) The announced risk must be of 50%

2) There is no absolute genotype/phenotype correlation (including in a very family)

3) There is no evidence of genetic anticipation

4) Medically assisted procreation should be offered in every DBA patient (women & men)

Take home messages

DBA is not only a pediatric disease and may be diagnosed in adult patients

DBA phenotype in adults pts remains in part to be described

DBA is associated with premature aging of the bone marrow

DBA is a cancer-prone disease and clinical guidelines are needed regarding cancer prevention Detection and treatment

Genetic counseling is difficult in DBA patients

Thank you for your attention

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MaRIH network: Reference centres for rare diseases

Patients associations

Acknowledgments: DBA French group

- *Pr. Lydie DA COSTA Isabelle Marie*
- *AFMB: DBA family support group*

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Reconnue par le Ministère de la Santé

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