Diagnostic des anémies hémolytiques

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Hémolyse

- Raccourcissement de la durée de vie des globules rouges (< 120 jours)
- **Intratissulaire** (*physiologique*) macrophages (foie, rate)
- **Intravasculaire** (*pathologique*, systématique si hémolyse massive)

Association fréquente

Hémolyse Intratissulaire	Hémolyse intravasculaire
↗ Bili NC	↘↘↘ **Haptoglobine**
↘ **Haptoglobine**	↗↗↗ LDH
	↗ Bili NC
	Hémoglobinémie **Hémoglobinurie (sans hématurie)**
↗↗ Réticulocytes	
Macrocytose (sauf thalassémie, drépanocytose, sphérocytose)	

Si Bili NC et Haptoglobine normales ➡ hémolyse improbabe

Hémolyse

↗ bili NC

↳ HzptoGb

↗ Reticulocytes

↳ Hb (Anémie)

réflexe

→ Intrinsèque :

↳ HzptoGb ??? LDH.

HémoCherie / HémoGbvie

↳ Urine Porto

Hémolyses, causes

Causes corpusculaires

Maladies de l'hémoglobine

- Drépanocytose
- Hémoglobines instables
- Thalassémies

Enzymopathies

Maladies de la membrane

- Constitutionnelles
- Acquises: HPN

Causes extracorpusculaires

Immunologiques

- Auto- ou alloimmunisation
- Médicaments

Toxiques : saturnisme, médicaments

Bactériennes : perfringens

Parasitaires : paludisme, babésiose

Mécaniques

Late entry in sickle cell disease: characteristics, prognosis and outcome. A monocentric series of 108 patients

Patient	Type of SCD	Clinical manifestations leading to SCD diagnosis	Age at last evaluation (years)	Complications occuring during follow-up
1	SC	ocular hemorrhage	43	retinopathy, ACS*
2	SS	ocular hemorrhage	45	right blindness, ACS, shoulder osteonecrosis, cardiopathy
3	SC	ocular hemorrhage	57	retinopathy, ACS, hip osteonecrosis, priapism
4	SC	ocular hemorrhage	26	hip osteonecrosis
5	SC	ocular hemorrhage	39	retinopathy, priapism
6	SS	ACS	30	ACS
7	SS	ACS	25	ACS, priapism, leg ulcer
8	SS	ACS	23	ACS
9	SS	ACS	37	ACS, hip osteonecrosis
10	SC	ACS	24	ACS
11	SC	hematuria	35	priapism
12	SC	hematuria	50	retinopathy, hip osteonecrosis,
13	SC	hematuria	35	Š
14	SC	stroke	46	Š
15	SC	stroke	48	ACS, hip, shoulder osteonecrosis, epidermidis staphylococcus septi.
16	SC	hip osteonecrosis	44	hip osteonecrosis
17	SC	knee chronic pain	50	retinopathy, hip, shoulder osteonecrosis
18	SS	priapism	37	retinopathy, priapism, leg ulcer
19	SS	leg ulcer	54	retinopathy, leg ulcer
20	SS	acute splenic sequestration	35	ACS

Godeau et al, ASH Annual congress 2004

Hemolyse post-transfusionnelle et drépanocytose

- Transfusion

2 à 6 % d'hémolyses post transfusionnelles

70%

30%

Allo-anticorps

Différence entre le phénotype érythrocytaire des donneurs et des receveurs

Pas d'anticorps détectables

30 % des drépanocytaires sont alloimmunisés

En cas d'une nouvelle transfusion dans 60% des cas un nouvel anticorps apparaitra

Hémolyse post transfusionnelles retardées (DHTR)

D'après Habibi et al

Absence de rendement transfusionnel

↓

99 épisodes chez 79 patients
26 grossesses
6 décès

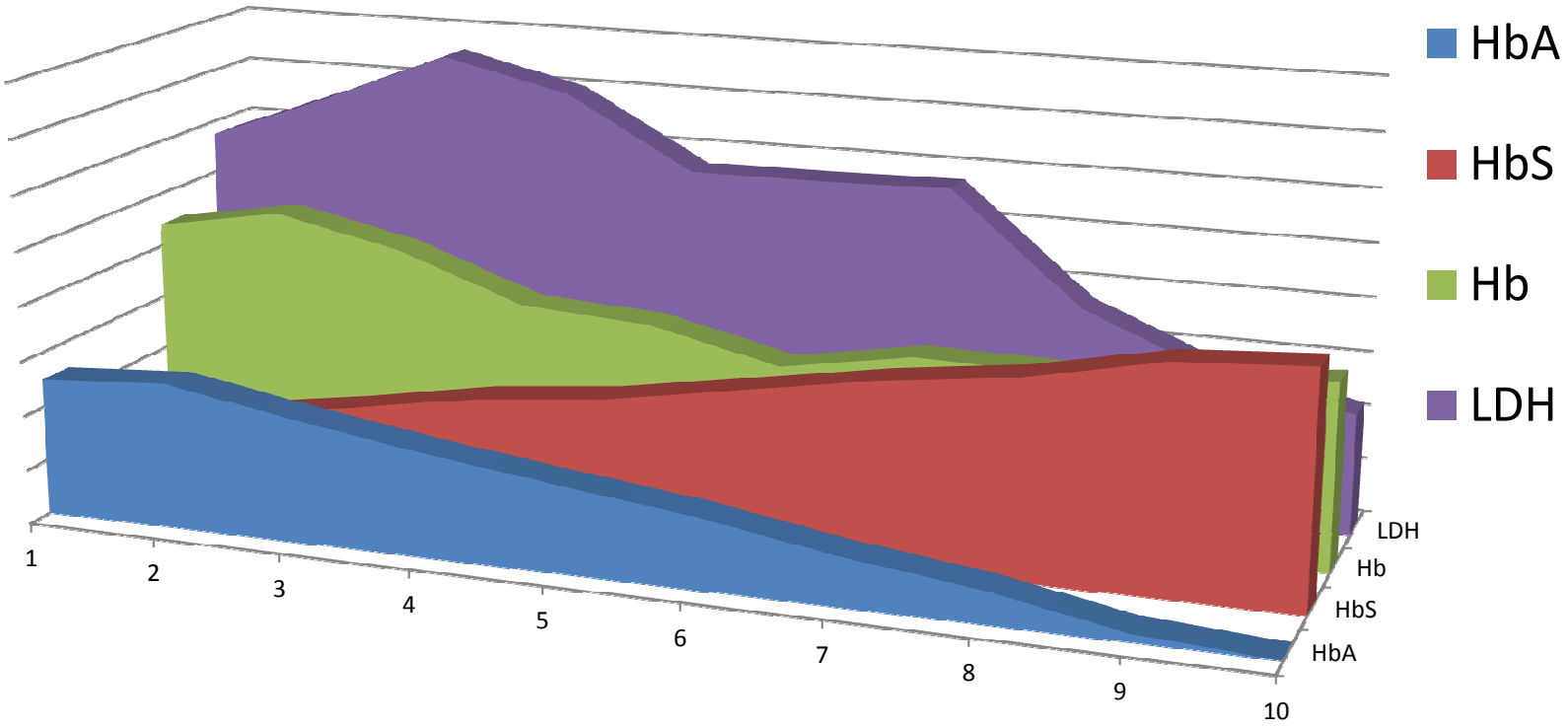
STA, Défaillance multiviscérale

Hémoglobinurie avec urines Porto. ↘ %HbA, ↘Hb, ↗ LDH
NE PAS RETRANSFUSER SAUF….

Hémolyses retardées post – transfusionnelles

- Diagnostic clinique: ***CVO très intenses***
- Présence de signes d'hémolyse intra-vasculaire
  - ***Ictère***
  - ***Urines très foncées***
  - ***Anémie***
  - ***Augmentation majeur des LDH***
  - ***Augmentation de BiliT***
- ***Survient <u>après transfusion</u> (Moyenne 9 jours)***

DHTR: un moyen simple de faire le diagnostic: électrophorèse de l'Hb

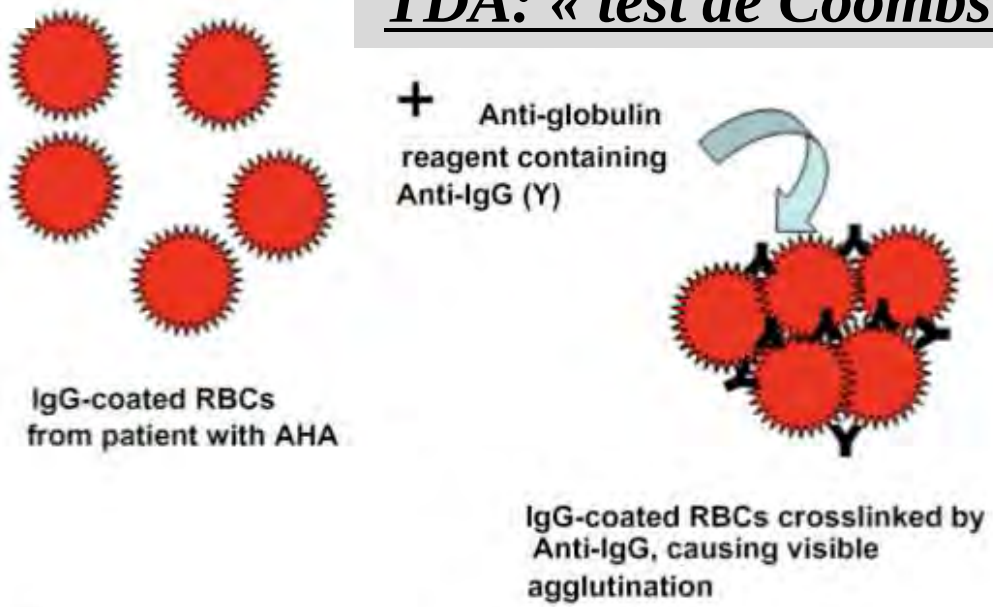


Chute rapide du taux d'HbA

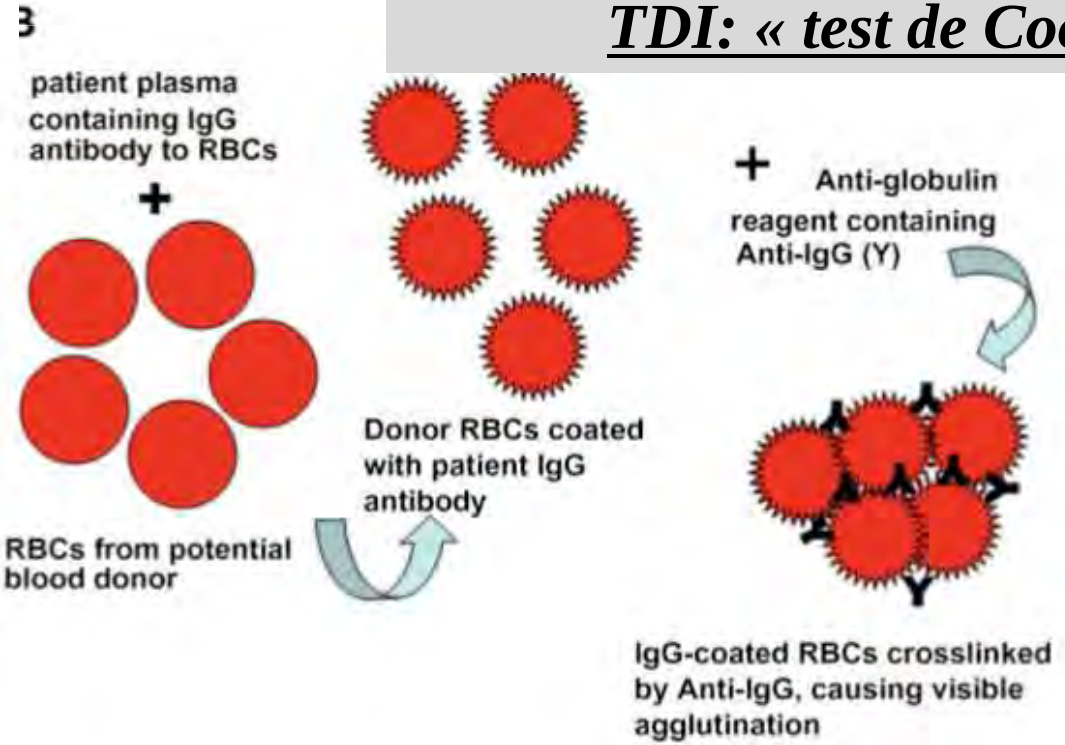
Les 2 examens essentiels et urgents

- Test de Coombs direct
- Frottis: présence de schizocytes ?

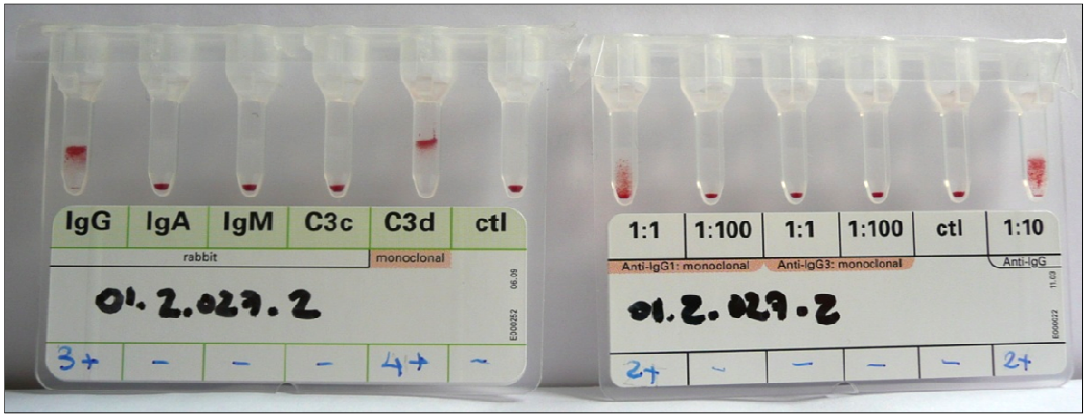
TDA: « test de Coombs direct »



TDI: « test de Coombs indirect »



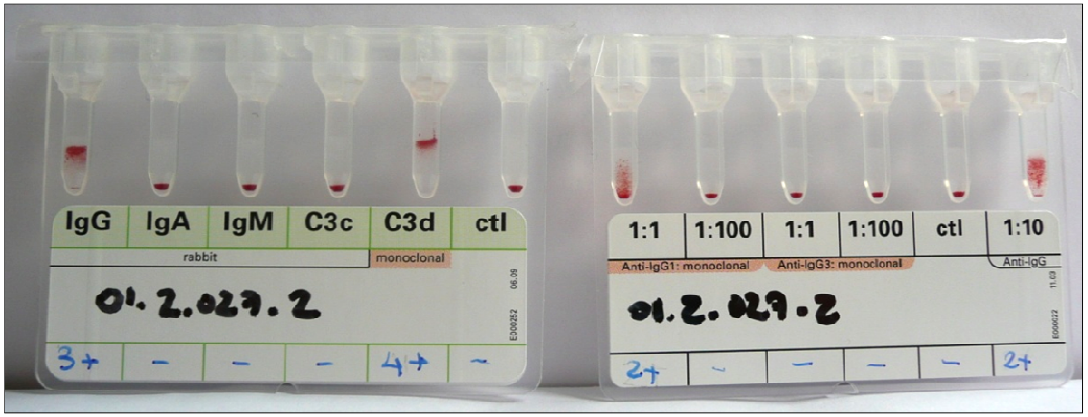
TDA
Sensibilité: 98-100%
Spécificité: 95%



- **TDA negatif ?:**
  - ***AutoAc en dessous du seuil de sensibilité***
  - ***Auto Ac d'isotype IgA ou IgM***
  - ***Auto Ac de basse affinité***
    - ***➔ utiliser des tests plus spécifiques: ELISA, Eluats, etc...***

TDA positif

Chaud ou froid ?



- **AHAI « chaudes » (75%)**
  - ***Test Coombs IgG-C ou IgG ± faible titre agglu froides***
- **AHAI « froides » (25%)**
  - ***Test Coombs C + Agglu froides fort titre***

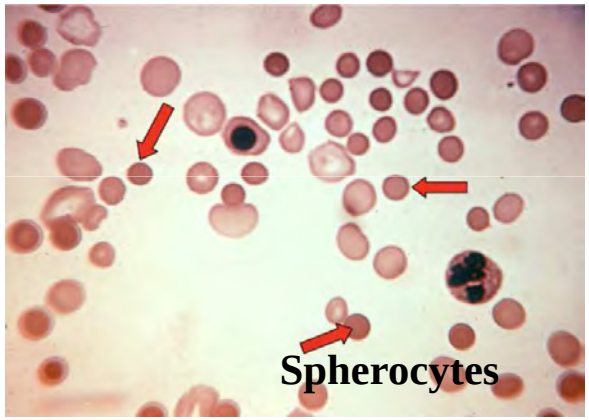
AHAI à Ac chaud, caractéristiques (1)

Test de Coombs de type **IgG-C** ou **IgG** seule avec parfois agglutinines froides

- Maladie orpheline (1/100 000/yr)
- Tous les âges mais souvent > 40 yrs
- **Maladies associées: > 50%**
- Sex ratio (F/M): 1.6
- Début insidieux *(mais pas toujours…)*
- Dyspnée, pâleur, ictère,
- Examen physique normal ou **splénomégalie**

AHAI à Ac chaud, caractéristiques(2)

- Anemie, macrocytose, sphérocytose
- **Réticulocytose *(inconstante)***
- Haptoglobine basse
- Elévation des LDH
- Hyperbilirubinemie NC
- Sphérocytose possible
- **Absence d'hémoglobinurie (sinon, reconsidérer le diagnostic)**



Caractéristiques de 60 patients adultes atteints d'AHAI auto Ac chauds

Roumier et al, Am J Hematol 2014, in press

caractéristiques	
Sex ratio	1/1
Age moyen	54 ± 22
Hb moyen (g/dL)	6,4 ± 1,7
Réticulocytes (G/L)	285 ± 174
VGM moyen (µL)	108 ± 14
Hapto basse	93%
LDH élevées	93%
Bilirubine élevée	82%
Présence de sphérocytes	41%
Test de Coombs direct	
- **IgG**	**40%**
- **IgG + C3d**	**55%**
- C3d	3%
- IgA	2%

Caractéristiques de 60 patients adultes atteints d'AHAI auto Ac chauds

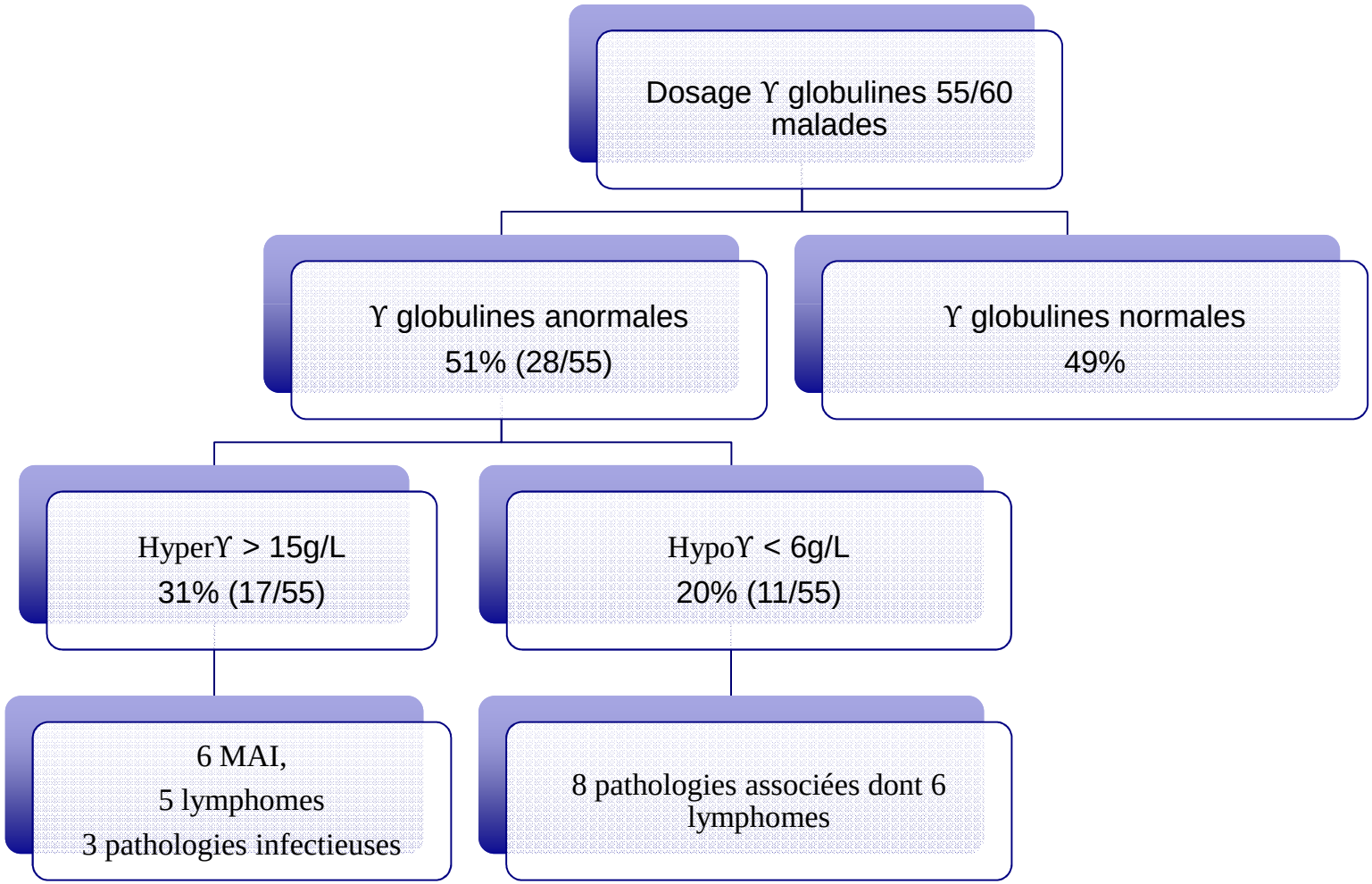
Roumier et al, Am J Hematol 2014, in press

caractéristiques	
Sex ratio	1/1
Age moyen	54 ± 22
Hb moyen (g/dL)	6,4 ± 1,7
Réticulocytes (G/L)	265 ± 147
VGM (fL)	103 ± 12
Hapto basse	93%
LDH élevées	93%
Bilirubine élevée	82%
Test de Coombs direct	
- IgG	40%
- IgG + C3d	55%
- C3d	3%
- IgA	2%

Recherche d'agglutinines froides chez 28 patients
Présentes dans 4 cas, titre de 1/64 à 1/512

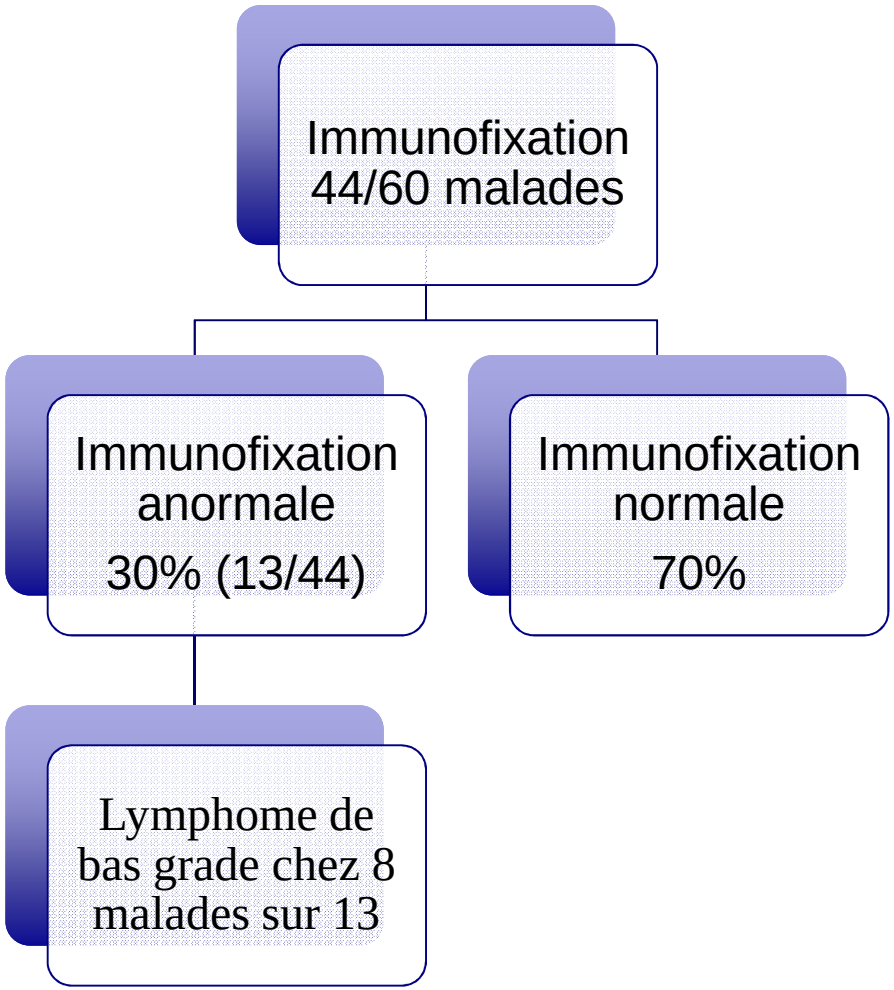
Caractéristiques de 60 patients adultes atteints d'AHAI auto Ac chauds

Roumier et al, Am J Hematol 2014, in press



Caractéristiques de 60 patients adultes atteints d'AHAI auto Ac chauds

Roumier et al, Am J Hematol 2014, in press



Caractéristiques de 60 patients adultes atteints d'AHAI auto Ac chauds

Roumier et al, Am J Hematol 2014, in press

Pathologies associées	
Hémopathies lymphoïdes	23%
Hémopathies lymphoïdes mal classées	10%
Maladies autoimmunes	13%
Autres	17%
AHAI isolée	35%

AHAI chaudes et Hémopathies (n=15/72)

Diagnostic de l'hémopathie / AHAI

Antérieur : 1

LLC

Simultané : 8

LNH B bas grade : 3
Waldenström : 1
LLC : 3
LAID : 1

Postérieur : 6

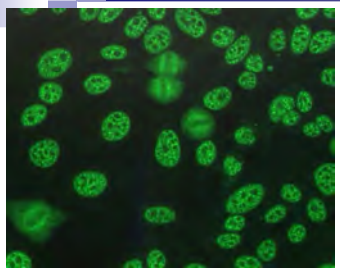
Hodgkin :1
LNH immunoblastique : 1
LNH centroblastique : 1
Waldenström : 1
Lymphome T : 1
LNH B bas grade : 1

Le diagnostic d'hémopathie lymphoïde peut être retardé
=> SURVEILLANCE

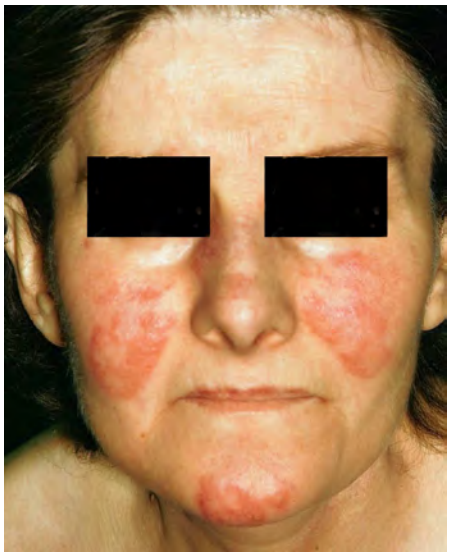
I Genty et al, Rev Med Interne 2002

LLC et AHAI

- AHAI « chaudes »
- La négativité du TDA n'élimine pas le Dg
- 2 à 4% des LLC
- Facteurs de risque
  - ***Age (> 65 ans)***
  - ***Sexe (plus fréquent chez l'homme)***
  - ***LLC à un stade avancé,***
  - ***Lymphocytes > 60 G/L***
  - ***Titre élevé de β2 microglobuline***
  - ***Absence de mutation IgVH***
- Valeur pronostique débattue
- Rôle de la fludarabine débattu



AHAI et Lupus



- AHAI « chaudes »
- 5 to 10%
- Anémie sévère 25%
- **Peut précéder le lupus +++**
- Facteurs de risque :
  - APL ?
  - Ethnies noires
  - Thrombopénie (Evans' syndrome)
  - Azathioprine (?)
- Pronostic
  - **N'influence pas le pronostic**
  - Mais associé avec atteintes sévères (neuro, rein…)

Autoimmune hemolytic anemia in patients with SLE

Kokori et al, Am J Med 2000; 108:198-204

41 patients,

Sex ratio (F/M): 4.1/1

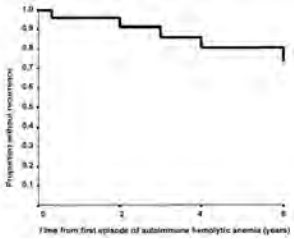
Warm AHA : 100%

66% occured at the onset of SLE

Low lupus activity index (ECLAM < 4)

Low risk of recurrence

High risk of thrombosis: 10 events (25%) with a follow-up of 4 ± 4 yrs



	Univariate models		Multivariate models	
	Odds ratio	P	Odds ratio	P
IgG cardiolipin	4.3 (2.1-9.3)	0.02	5.8 (1.4-24)	0.01
Thrombosis	2.3 (0.7-7.3)	0.2	4.6 (1-21)	0.05

Autoimmune Hemolytic Anemia in Patients with Systemic Lupus Erythematosus

Styliani I. G. Kokori, MD, John P. A. Ioannidis, MD, Michalis Voulgarelis, MD, Athanasios G. Tzioufas, MD, Haralampos M. Moutsopoulos, MD

PURPOSE: We sought to evaluate the clinical and serologic associations with, and outcomes of, autoimmune hemolytic anemia, as compared with other types of anemia, in patients with systemic lupus erythematosus (SLE).

SUBJECTS AND METHODS: We studied 41 consecutive patients with SLE with clinically manifest autoimmune hemolytic anemia, including 27 (66%) in whom hemolysis was the initial disease manifestation. We matched each patient for age and disease duration with a patient with SLE with anemia resulting from a different cause.

RESULTS: The 41 patients had a total of 50 episodes of autoimmune hemolytic anemia. The recurrence rate was 4 per 100 person-years. Cases and controls had similar mean (± SD) lupus activity indexes (2.1 ± 1.5 vs 2.4 ± 1.3, $P = 0.5$). Patients with autoimmune hemolytic anemia at any time could be distinguished from patients with other causes of anemia, because they were more likely to have elevated titers of IgG anticardiolipin antibodies (odds ratio (OR) = 5.8; 95% confidence interval (CI), 1.4 to 24) and thrombosis (OR = 4.6; 95% CI, 1.0 to 21). Autoimmune hemolytic anemia at the onset of SLE was independently associated with renal involvement (OR = 5.4; 95% CI, 1.0 to 28), thrombocytopenia (OR = 7.3; 95% CI, 1.1 to 48), and possibly thrombotic episodes during follow-up (OR = 11; 95% CI, 0.8 to 160) when compared with controls with other types of anemia at the onset of SLE.

CONCLUSIONS: Autoimmune hemolytic anemia usually occurs at the onset of SLE, and its recurrence rate is low among treated patients. The association with IgG anticardiolipin antibodies and thrombosis suggests that the occurrence of autoimmune hemolytic anemia may define a subgroup of patients with SLE who have characteristic serologic and clinical manifestations. Am J Med. 2000;108:198–204. ©2000 by Excerpta Medica, Inc.

Patients with systemic lupus erythematosus (SLE) may develop several hematologic complications, including anemia, leukopenia, and thrombocytopenia (1,2). Anemia can have many causes, including autoimmunity (3,4). Several case series (5–11) have shown that autoimmune hemolytic anemia occurs in approximately 10% of patients with SLE. It may be the sole presenting sign of the disease and may predate the appearance of other disease manifestations by several years (3). Autoimmune hemolytic anemia can also be part of the antiphospholipid syndrome, which is associated with high titers of anticardiolipin antibodies, thrombosis, thrombocytopenia, and recurrent fetal loss (12).

However, the clinical importance and the clinical and serologic associations of autoimmune hemolytic anemia in SLE are controversial. There is substantial uncertainty about whether hemolysis portends a more severe (9,13) or more benign (6,8) prognosis. Moreover, the effects of, and risk factors for, autoimmune hemolytic anemia have not been evaluated using controls with SLE who have other types of anemia. Hence, the aim of this study was to evaluate the clinical and serologic associations with, and prognosis of, patients with SLE and autoimmune hemolytic anemia. From within a large cohort of consecutive patients with SLE, we identified those with autoimmune hemolytic anemia and compared them with patients with other types of anemia.

MATERIAL AND METHODS

Patients were seen at the Department of Pathophysiology, School of Medicine, National University of Athens, from November 1994 to October 1998. All patients fulfilled at least four of the revised American College of Rheumatology criteria for the diagnosis of SLE (14). We considered patients to have active autoimmune hemolytic anemia if they had a decrease of at least 3 g/dL in their hemoglobin level, an increase in the serum unconjugated bilirubin level of at least 0.6 mg/dL, a reticulocyte count of 5% or greater corrected for hemoglobin levels, and a positive direct Coombs' test by direct antiglobulin test using polyspecific anti–human immunoglobulin and anticomplement antibodies (Ortho Diagnostics, Inc, Raritan, New Jersey). We also required that other causes of hemolysis, including hereditary, drug-induced, microangiopathic hemolytic anemia, had been excluded.

We identified patients who developed autoimmune hemolytic anemia at the onset of SLE, or in whom it oc-

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Bilan à réaliser devant une AHAI à autoAc chauds

- AAN
- EPP, dosage pondéral des Ig
- Immunofixation
- Phénotypage des lymphocytes circulants
- Scanner TAP
- Sérologies virales HBV/HCV/VIH
- **BM non systématique**

The spectrum of Evans syndrome in adults: new insight into the disease based of the analysis of 68 cases

Michel et al, Blood 2009; 114: 3167-72

- AHAI « chaude »
- Cytopénies souvent marquées et symptomatiques
- Maladie associée dans 50% des cas
- Délai entre les deux cytopénies parfois prolongé
- Evolution sévère
- Mortalité élevée (25%)

CLINICAL TRIALS AND OBSERVATIONS

The spectrum of Evans syndrome in adults: new insight into the disease based on the analysis of 68 cases

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Evans syndrome (ES) is a rare disease characterized by the simultaneous or sequential development of autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) and/or immune neutropenia. To better describe the characteristics and outcome of ES in adults, a survey was initiated in 2005. The data from 68 patients (60% of them women) fulfilling strict inclusion criteria for ES are reported. The mean age at time of ITP and/or AIHA onset was 52 plus or minus 33 years, both cytopenias occurred simultaneously in 37 cases (54.5%). ES was considered as "primary" in 34 patients (50%) but was associated with an underlying disorder in half of the cases, including mainly systemic lupus, lymphoproliferative disorders, and common variable immunodeficiency. All patients were given corticosteroids, but 50 of them (73%) required at least one "second-line" treatment, including splenectomy(n = 19) and rituximab (n = 11). At time of analysis, after a mean follow-up of 4.8 years, only 22 patients (32%) were in remission off treatment; 16 (24%) had died. In elderly patients, the risk of cardiovascular manifestations related to AIHA seems to be higher than the ITP-related risk of severe bleeding. In conclusion, ES is a potentially life-threatening condition that may be associated with other underlying autoimmune or lymphoproliferative disorders. (Blood. 2009;114:3167-3172)

Introduction

Evans syndrome (ES), which was first described in 1951, is an autoimmune disorder characterized by the simultaneous or sequential development of autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) and/or immune neutropenia in the absence of any underlying cause.[1] Although ES has been since its first description considered or defined as an "idiopathic" condition and thus mainly as a diagnosis of exclusion, ES may be associated with or show other diseases or conditions such as systemic lupus erythematosus (SLE),[2] lymphoproliferative disorders,[3,4] or primary immunodeficiencies.[5] In childhood, ES may also show an autoimmune lymphoproliferative syndrome (ALPS), a disorder of disrupted lymphocyte homeostasis related to some mutations in the Fas apoptotic pathway.[6] ES is a rare condition because it is diagnosed in only 0.8% to 3.7% of all patients with either ITP or AIHA at onset.[7] Few and mainly pediatric data on ES are available in the literature[8-11]; therefore, the characteristics and outcome of adult's ES are poorly known. Moreover, because there have been no prospective or randomized controlled trials, the management of ES is based on empirical data, and it is mainly based on indirect evidence extrapolated from the "standard of care" in primary ITP or AIHA or both.

To better define the clinical spectrum of ES in adults and to describe the main characteristics and outcome of this rare condition, a survey was initiated in 2005 throughout the Working Group on Thrombocytopenias of the European Hematology Association. The data of 68 cases of ES included in this registry are reported here.

Methods

Patients

This retrospective cohort study was initiated in the department of Internal Medicine at Henri Mondor University Hospital (Créteil, France), a tertiary national referral center for adult autoimmune cytopenias. The study was then extended to 7 other centers in France (n = 5 departments of internal medicine) and Italy (n = 4 departments of hematology-oncology) throughout the Working Group on Thrombocytopenias of the European Hematology Association.

All consecutive patients with the diagnosis of ES in 1 of the 8 participating centers over a 15-year period and fulfilling the following eligibility criteria were included: age 16 years or more at diagnosis; ES defined by the occurrence (either simultaneously or sequentially within at least a 10-year period of time) of AIHA and ITP or autoimmune neutropenia. AIHA was defined by a hemoglobin (Hb) level of 11 g/dL or less at diagnosis with features of hemolysis (low haptoglobin level and/or increased LDH and/or bilirubin level) and a positive direct antiglobulin test (DAT) or when the DAT was negative, after the exclusion of any other cause of acquired or hereditary hemolytic anemia. ITP was defined according to American Society of Hematology criteria,[12] and only patients with a platelet count below 100 × 10⁹/L on 2 separate occasions were included. In case of concomitant active AIHA, the presence of a mild splenomegaly was not an

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- Evolution sévère
- Mortalité élevée (25%)
- Plusieurs lignes thérapeutiques requises
- Dépendance au traitement fréquente
- Avec recul de 4,8 ans, 32% des patients en rémission sans Tt

Table 4. Causes of deaths, n = 16

Causes of death	n
Infection	7
Septic shock (n = 6) due to *Staphylococcus aureus* (1), *Pseudomonas aeruginosa* (1),* unknown bacteria (4)†; one patient with a prior history of stroke had a fatal aspiration pneumonia	
Cancer	3
Site of cancer: uterus (1), pancreas (1), esophagus (1)	
Cardiovascular	3
Stroke (2), myocardial infarction (1)	
Myelodysplastic syndrome (RAEB)	1
B-cell non-Hodgkin lymphoma	1
Unknown	1

RAEB indicates refractory anemia with excess of blasts.
*A concomitant hemorrhagic stroke was suspected at time of death.
†Two of these patients had undergone a splenectomy 3 weeks and 2 years prior to death, respectively.

Michel et al, Blood 2009; 114: 3167-72

Maladie des agglutinines froides

Test de Coombs de **type C** avec **agglutinines froides**

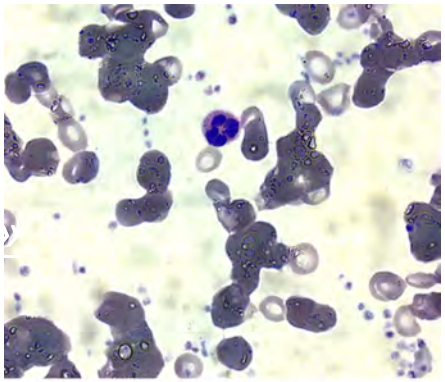

Fig. 1. Peripheral blood smear from a patient with primary CAD.

- Maladie, « clonale ».
  - IgMκ dans 90% des cas
  - BM : lymphome lymphoplasmocytique ou zone marginale => Waldenstroem (50%)
- Age médian 67 ans
- Pronostic favorable
- Espérance de vie similaire à celle de la population générale
- Poussées d'hémolyse (infection, exposition au froid)
- **Traitement le plus souvent nécessaire:** « not an indolent disease »
  - Transfusion 50%
  - Autre

Sigbjørn Berentsen
Elling Ulvestad
Ruth Langholm
Klaus Beiske
Henrik Hjorth-Hansen
Waleed Ghanima
Jon Hjalmar Sørbø
Geir E. Tjønnfjord

Lymphoproliferative Disorders • Research Paper

Primary chronic cold agglutinin disease: a population based clinical study of 86 patients

- Survie médiane: 12.5 ans
- Transformation LNH

Agressif : 3.5 % à 10 ans

Table 3. Bone marrow histology.

	n	%
Normal/reactive lymphocytosis	7	11
Irregular lymphoid hyperplasia	9	13
Non-Hodgkin's B-cell lymphoma	50	76
Lymphoplasmacytic lymphoma	*33*	*50*
Marginal zone lymphoma	*5*	*8*
Small lymphocytic B-cell lymphoma/ Chronic lymphocytic leukemia	*4*	*6*
Clonal lymphocytosis/ other small B-cell lymphoma	*8*	*12*
Total	66	100

76 %

Drug induced immune haemolytic anemia in the Berlin Case-control surveillance study

Garbe et al, Br J Haematol, 2011; 154: 644-53

assessment of individual cases. The spectrum of drugs suspected to cause IHA is similar to that reported in the literature (Salama *et al*, 1996). In principle, any drug may induce IHA. In each case of newly diagnosed IHA a drug aetiology should be considered and a careful history of medication must be taken.

- **Diclofenac**
- **Fludarabine**
- **Oxaliplatin**
- **Ceftriaxone**
- **Piperacillin**

- β-lactam antibiotics
- Cotrimoxazole
- Ciprofloxacin
- Lorazepam

bjh research paper

Drug induced immune haemolytic anaemia in the Berlin Case-Control Surveillance Study

Edeltraut Garbe,[1,2] Frank Andersohn,[3] Elisabeth Bronder,[2] Andreas Klimpel,[2] Michael Thomae,[4] Hubert Schrezenmeier,[5] Martin Hildebrandt,[6] Ernst Späth-Schwalbe,[7] Andreas Grüneisen,[8] Beate Mayer,[9] Abdulgabar Salama[10] and Hanife Kurtal[2]

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Summary

Drug-induced immune haemolytic anaemia is a rare but serious condition. This study investigated the possibility of drug aetiology of immune haemolytic anaemia (IHA) in 134 patients with new onset of IHA who were identified in the Berlin Case-Control Surveillance Study between 2000 and 2009. Single drugs related to IHA in three or more patients and assessed more than once as a certain or probable cause of IHA in a standardized causality assessment included diclofenac, fludarabine, oxaliplatin, ceftriaxone and piperacillin. In a case-control study including all 124 IHA cases developed in outpatient care and 731 controls, significantly increased odds ratios (OR) were observed for beta-lactam antibiotics (OR = 8·8; 95% confidence interval [CI] 3·2–25·2), cotrimoxazole (OR = 6·5; CI 1·1–37·9), ciprofloxacin (OR = 6·9, CI 1·3–38·3), fludarabine (OR = 22·2; CI: 2·8–454·5) and lorazepam (OR = 5·3; CI: 1·2–21·2). Excluding new onset cases with a chronic IHA disease course, an increased risk became also apparent for diclofenac with an OR of 3·1 (CI 1·3–7·0). This is the first case-control study investigating drugs as risk factors for IHA. It corroborates an increased risk for several drugs that have been implicated as a cause of IHA in the standardized causality assessment of individual cases.

Keywords: Berlin case-control surveillance study, immune haemolytic anaemia, drug-induced, causality assessment, case-control study.

Drug-induced immune haemolytic anaemia (DIIHA) is a serious, but rare condition with an estimated incidence of approximately one case per million inhabitants per year (Petz & Garratty, 2004). A substantial number of fatal cases have been described in case reports, case series and reviews (Garratty et al. 1991, 1992; Meyer et al. 1999; Seltsam & Salama, 2000; Ahrens et al, 2002; Garratty, 2010; Yürek et al, 2010). Both the antidepressant nomifensine and the liver protectant clanidanol have been withdrawn from the market because of their implication in DIIHA (Salama, 2009). DIIHA

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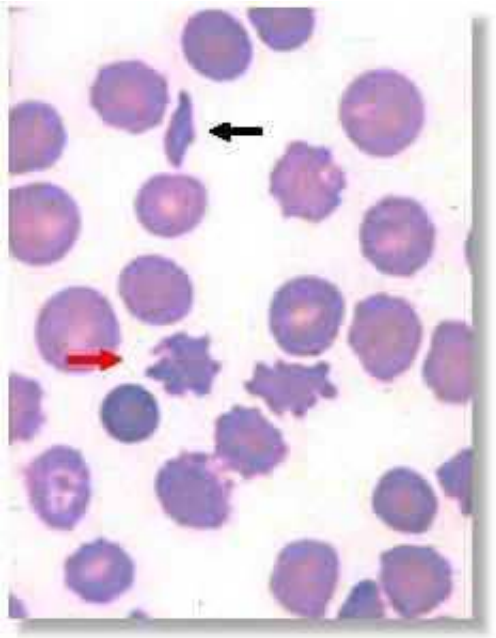
bjh British Journal of Haematology

Les 2 examens essentiels et urgents

- Test de Coombs direct
- **Frottis: présence de *schizocytes ?***



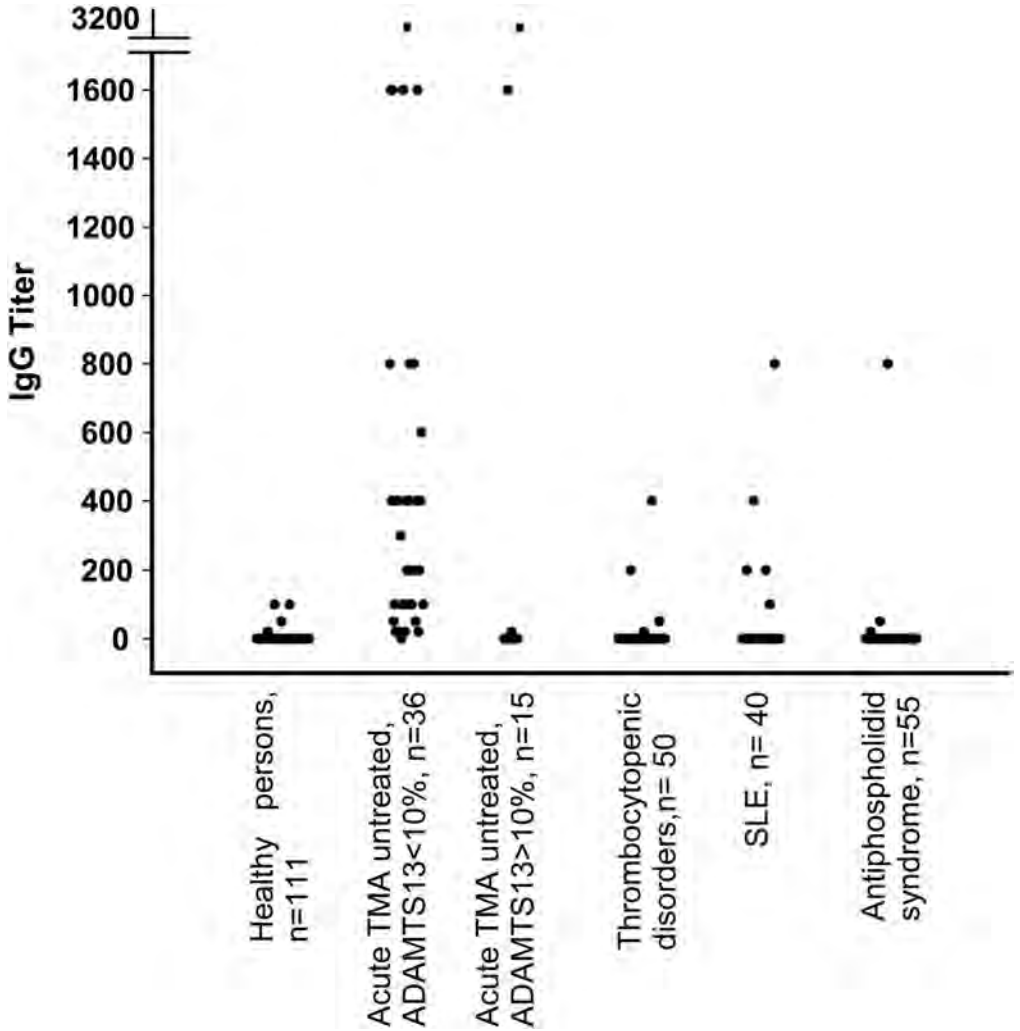
PTT (Sd de Moschcowitz)

- Hémolyse (100 %)
- Thrombopénie (≈ 100 %)
- Signes neurologiques (90 %)
- Atteinte rénale
- Fièvre

Pentade présente dans 40 % des cas

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Figure 1. Anti-ADAMTS13 IgG antibody titers in healthy donors, patients with TMA, thrombocytopenic disorders, and autoimmune diseases other than TMA



Rieger, M. et al. Blood 2005;106:1262-1267

ARTHRITIS & RHEUMATISM
Vol. 54, No. 8, August 2006, pp 2568–2576
DOI 10.1002/art.22018

Mortality in the Catastrophic Antiphospholipid Syndrome

Causes of Death and Prognostic Factors in a Series of 250 Patients

Silvia Bucciarelli,[1] Gerard Espinosa,[1] Ricard Cervera,[1] Doruk Erkan,[2] José A. Gómez-Puerta,[1] Manuel Ramos-Casals,[1] Josep Font,[1] and Ronald A. Asherson,[3] for the CAPS Registry Project Group (European Forum on Antiphospholipid Antibodies)

Table 4. Laboratory features of patients with CAPS, categorized according to their death or survival*

	Patients who died during a CAPS episode (n = 114)	Patients who survived a CAPS episode (n = 136)
Disseminated intravascular coagulation	15/90 (16.7)	18/131 (13.7)
Hemolysis	33/101 (32.7)	42/119 (35.3)
Thrombocytopenia (≤100,000 platelets/mm^3)	34/86 (39.5)	54/101 (53.4)
Schistocytes	9/78 (11.5)	20/108 (18.5)
Antinuclear antibodies	62/94 (65.9)†	56/114 (49.1)
Antiphospholipid antibodies		
IgG aCL	87/103 (84.5)	110/133 (82.7)
IgM aCL	35/92 (38)	57/129 (44.2)
Lupus anticoagulant	78/97 (80.4)	95/126 (75.4)

* Values are the number of patients/number tested (%). CAPS = catastrophic antiphospholipid syndrome; aCL = anticardiolipin antibodies.
† $P = 0.017$ versus the group that survived.

Observation (1)

- Femme 34 ans
- Asthénie majeure isolée
- Hb 3g/dL, VGM: 102 µ3
- Réticulocytes: 91x10^9/L
- Plaquettes: 40x10^9/L
- **Schizocytose majeure** (25 % des hématies)
- LDH: 5700 UI/L
- Haptoglobine: 0.06 g/L
- Test de Coombs négatif

PTT ?

Observation (1)

- Femme 34 ans
- Asthénie majeure isolée
- Hb 3g/dL, **VGM: 102 µ3**
- **Réticulocytes: 91x10^9/L**
- Plaquettes: 40x10^9/L
- Schizocytose majeure (25 % des hématies)
- LDH: 5700 UI/L
- Haptoglobine: 0.06 g/L
- Test de Coombs négatif

PTT ?

Observation (2)

- ***Vitamine B12: 35 ng/L (N > 200)***
- Folates sériques: Nx
- Folates globulaires: 180 µg/L (N > 200)
- Homocystéine: 170 µmol/L (N < 16)
- Myélogramme: mégaloblastose

Piège à folates

Penser à une carence en B12 devant un tableau de MAT !

Observation n° 2 (1)

- Femme 67 ans
- Valve mécanique en position mitrale
- Hb: 5,6 g/dL
- Haptoglobine < 0,05 g/dL
- Réticulocytes: 250x10^9/L
- Test de Coombs négatif
- **Schizocytes présents**
- Echo cœur: *valve mécanique OK…*

Observation n° 2 (2)

- Diagnostic d'AHAI à Coombs négatif…
- Echec corticoïdes
- Echec azathioprine
- Transfusions itératives et plusieurs épisodes d'OAP
- Nouvelles écho cœur: *pas de dysfonction de valve…*
- **Schizocytes toujours présents**
- *Discussion de splénectomie…*

Observation n° 3 (3)

Chirurgie thoracique préférée à la splénectomie !

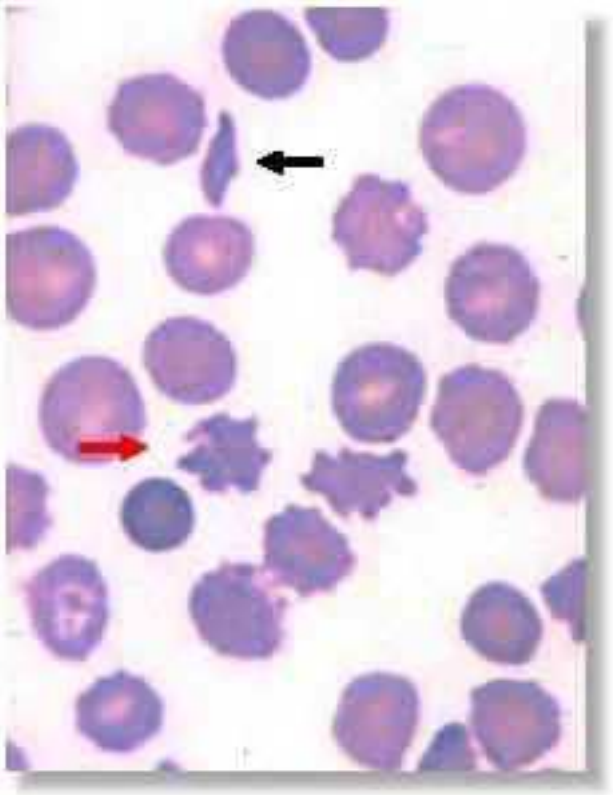
→ désinsertion de valve mécanique !
disparition de l'hémolyse…

Attention au diagnostic d'AHAI à Coombs négatif +++

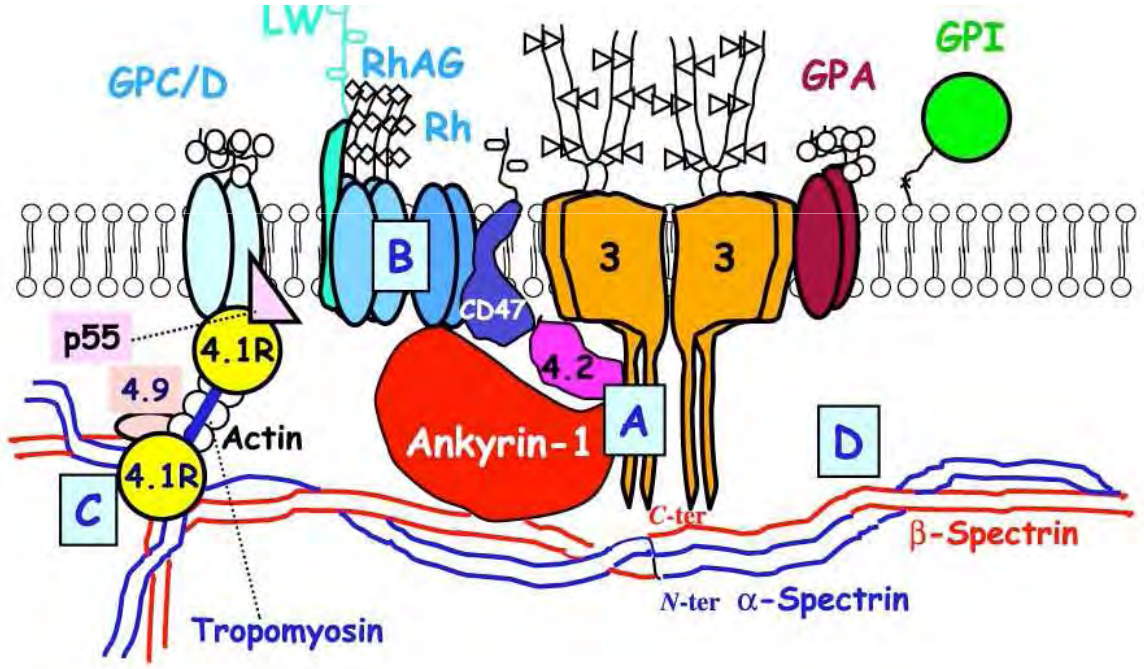
Penser à la désinsertion de valve mécanique +++

Etiologies des schizocytoses

1) Valves mécaniques, RA serré
2) MAT
   - PTT (LED, Mt, infection, BMT)
   - HELLP
   - SHU
3) Métastastases osseuses
4) HTA maligne, éclampsie, CAPS
5) Carences folates/B12



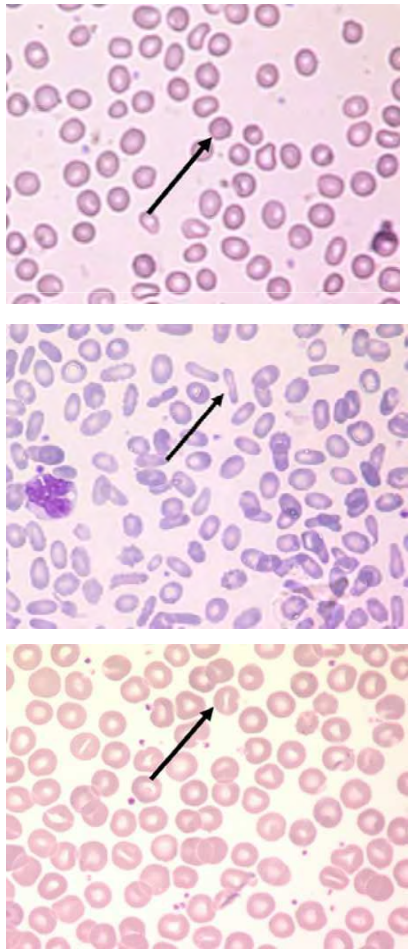
Les maladies de la membrane constitutionnelles



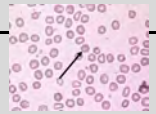
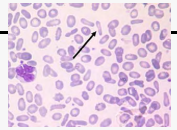
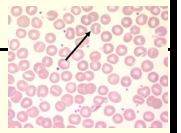
D'après Delaunay, Blood Review, 2007; 21:1-20

Les maladies de la membrane constitutionnelles

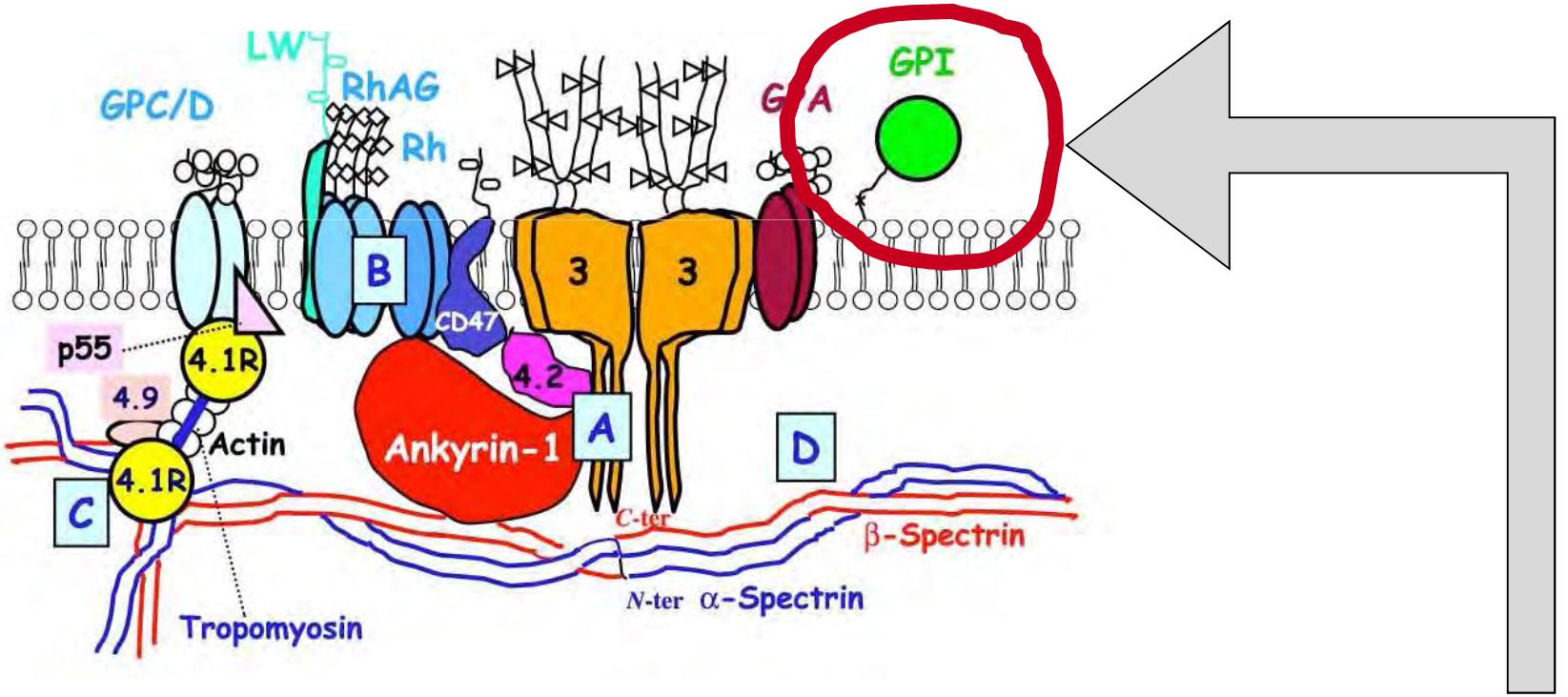
- Sphérocytose
- Ellipsocytose
- Stomatocytose



D'après Delaunay, Blood Review, 2007; 21:1-20

	Sphérocytose	Ellipsocytose	Stomatocytose
Transmission	Dominante (75% des cas) 	Dominante 	Dominante 
Fréquence	1:1000-2500	1:2500-4000	1:30 000-100 000
Répartition géographique	Ubiquitaire	Afrique, Méditerranée	Ubiquitaire
S. cliniques	**Hémolyse** Lithiase, érythroblastopénie, aggravation si infection	**Hémolyse** Lithiase, érythroblastopénie, aggravation si infection	**Hémolyse** **Thrombose**
Diagnostic	**Cytométrie de flux (test EMA)** Ektacytométrie Génétique	**Cytométrie de flux** Ektacytométrie Génétique	**Ektacytométrie**
Splénectomie ?	OUI	OUI/NON	**NON !**

Hémoglobinurie paroxystique nocturne (« HPN »)



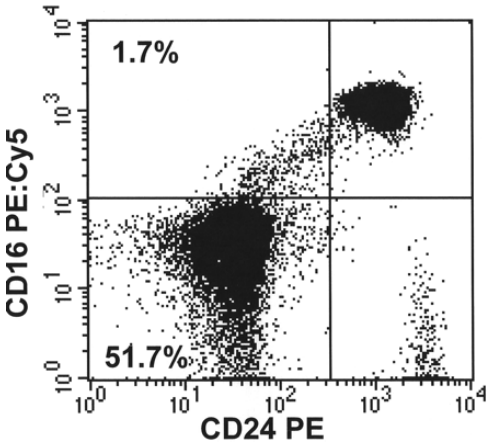
Déficit des protéines d'ancrage du CD55 et CD59

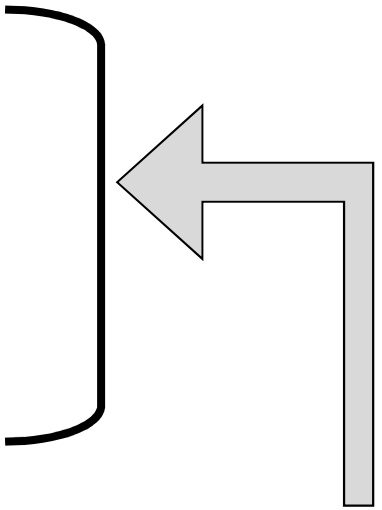
HPN

- Mutation du gène PIG-A (chromosome X)
- Défaut d'expression **CD55**

  (*decay accelerating factor*)
- Défaut d'expression **CD59**

  (*membrane inhibitor of reactive lysis*)





Hypersensibilité à l'action lytique du complément

HPN, manifestations cliniques

- **Hémolyse intravasculaire**
  - ***Hémolyse, urines rouges***
  - ***Asthénie***
- **Thromboses veineuses**
  - ***Sites inhabituels***
  - ***Peuvent être révélatrices***
- **Carence en NO**
  - ***Dysérection***
  - ***Douleurs abdominales, spasme oesophagien***
- **Insuffisance médullaire**

Caractéristiques de l'HPN: registre international de 1610 patients

Schrezenmeir et al, Haematologica 2014; 99:5

Caractéristiques	
Femme	53%
Age de début	32 ans (3-87)
Hb (g/dL)	10,6
LDH (x VN)	1,96
% clone HPN	68%
Thrombose	15%
Atteinte rénale	14%
Fatigue	80%
Dypnée	64%
Hémoglobinurie	62%
Douleurs abdominales	44%
Douleurs thoraciques	33%
Dyfonction érectile	30%

ARTICLES

Paroxysmal Nocturnal Hemoglobinuria

Baseline characteristics and disease burden in patients in the International Paroxysmal Nocturnal Hemoglobinuria Registry

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ABSTRACT

Paroxysmal nocturnal hemoglobinuria is a rare, acquired disease associated with hemolytic anemia, bone marrow failure, thrombosis, and, frequently, poor quality of life. The International PNH Registry is a worldwide, observational, non-interventional study collecting safety, effectiveness, and quality-of-life data from patients with a confirmed paroxysmal nocturnal hemoglobinuria diagnosis or detectable paroxysmal nocturnal hemoglobinuria clone, irrespective of treatment. In addition to evaluating the long-term safety and effectiveness of eculizumab in a global population, the registry aims to improve diagnosis, optimize patient management and outcomes, and enhance the understanding of the natural history of paroxysmal nocturnal hemoglobinuria. Here we report the characteristics of the first 1610 patients enrolled. Median disease duration was 4.6 years. Median granulocyte paroxysmal nocturnal hemoglobinuria clone size was 68.1% (range 0.01-100%). Overall, 16% of patients had a history of thrombotic events and 14% a history of impaired renal function. Therapies included anticoagulation (31%), immunosuppression (19%), and eculizumab (25%). Frequently reported symptoms included fatigue (80%), dyspnea (64%), hemoglobinuria (62%), abdominal pain (44%), and chest pain (33%). Patients suffered from poor quality of life, 28% of patients had been hospitalized due to paroxysmal nocturnal hemoglobinuria-related complications and 17% stated that paroxysmal nocturnal hemoglobinuria was the reason they were not working or were working less. This international registry will provide an ongoing, valuable resource to further the clinical understanding of paroxysmal nocturnal hemoglobinuria. (*Clinicaltrials.gov identifier:01374360*)

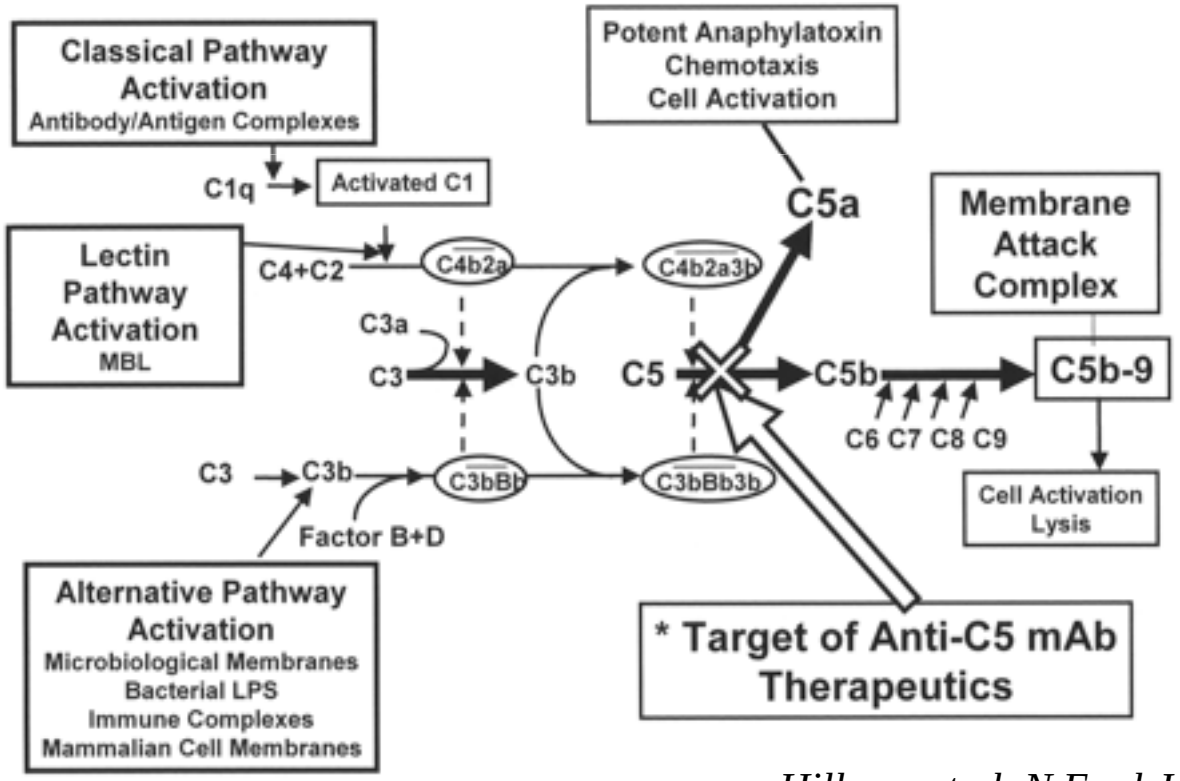
Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired disease characterized by chronic intravascular hemolysis caused by uncontrolled complement activation. The cellular abnormality in this life-threatening disease originates from a mutation in the phosphatidylinositol glycan class A (*PIGA*) gene, resulting in a deficiency of glycosylphosphatidyl inositol (GPI)-anchored complement regulatory proteins, including CD55 and CD59, on the surface of blood cells.[1] Patients with chronic hemolysis experience a marked increased risk of thromboembolism (TE), which may ultimately lead to target organ damage and death.[2,3] Retrospective analyses have reported that, despite best supportive care, the 10-year survival rate in patients with PNH ranged from 50% for patients diagnosed between 1940 and 1970[4] to 75% in a more recent series.[5] TE is the leading cause of mortality in patients with PNH, accounting for between 40% and 67% of deaths with known causes.[6] Patients with PNH also experience symptoms including fatigue, abdominal pain, headache, shortness of breath, dysphagia, and erectile dysfunction.[7] These symptoms can be debilitating and significantly reduce the quality of life (QoL) of patients with PNH.[8] PNH may develop in the absence of another bone marrow disorder (BMD), as a condition secondary to BMDs such as aplastic anemia (AA) or myelodysplastic syndrome, or as subclinical PNH.

The only potentially curative therapy for PNH is allogeneic bone marrow transplantation; however, this procedure is associated with substantial morbidity and mortality[9,10] and, consequently, is not an appropriate therapeutic option for most patients. Historically, management of PNH was limited to the use of supportive measures such as blood transfusions and anticoagulation therapy. However, it has been reported that the risk of TE in patients with PNH remains high even in patients who have no clinical evidence of TE or are receiving prophylactic anticoagulation,[11] which is itself associated with an increased risk of bleeding complications.[12] In one

©2014 Ferrata Storti Foundation. This is an open-access paper. doi:10.3324/haematol.2013.093161
The online version of this article has a Supplementary Appendix.
Manuscript received on June 12, 2013. Manuscript accepted on January 29, 2014.
Correspondence: peter.hillmen@nhs.net

Eculizumab: Ac monoclonal humanisé inhibant la cascade du complément



Hillmen et al, N Engl J Med 2004

Enzymopathies

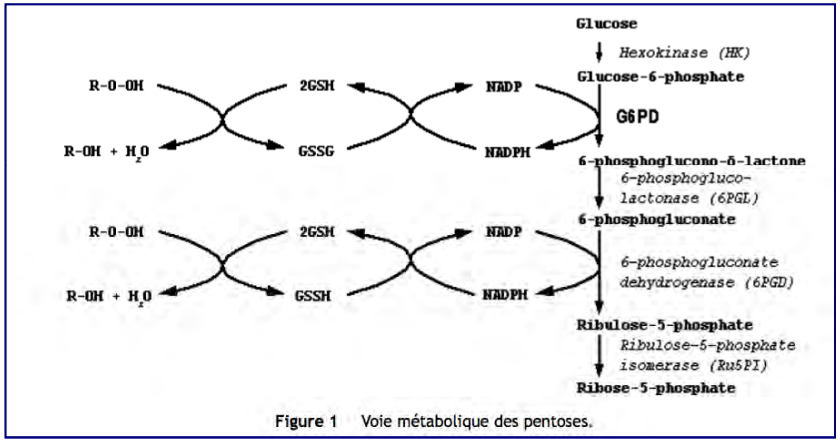
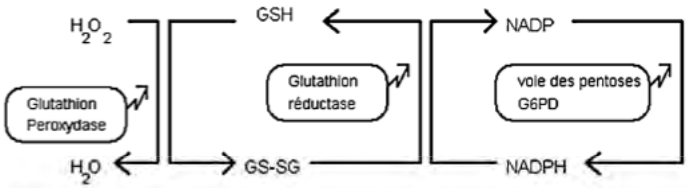


Figure 1 Voie métabolique des pentoses.

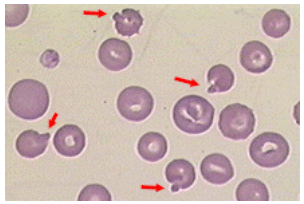


GSH : glutathion réduit
GSSG : glutathion oxydé

Figure 2 Métabolisme du gluthation : la glucose-6-phosphate déshydrogénase (G6PD) est l'enzyme centrale de la cascade antioxydante du globule rouge. Le gluthation détoxifie la cellule des molécules de peroxyde d'hydrogène grâce à la gluthation peroxydase. Le gluthation ainsi oxydé est recyclé par la glutha-tion S-transférase et la gluthation réductase. La nicotinamide adénine dinucléotide phosphate réduite (NADPH) permettant la réduction du gluthation est fournie grâce à la voie des pentoses et donc à la G6PD. Le ratio gluthation oxydé (GSSG)/gluthation réduit (GSH) est de 100/1.

Déficit en G6PD

- Fréquence +++ (400 millions …)
- Répartition ubiquitaire
- G6PD => Réduction du glutathion => lutte contre le stress oxydatif
- Précipitation de l'Hb



corps de Heinz

- G6PD: gène situé sur le chromosome X
- 300 variants

Déficit en G6PD, phénotype variable

- **Hémolyse intermittente +++**
  - ***Favisme***
  - ***Infection***
  - ***Médicaments:***
    - **Sulfamides**
    - **Quinolones**
    - **Antipaludéens**
  - ***IDM ?, Diabète ?***
- **Hémolyse chronique**
- **Absence d'hémolyse**

Déficit en G6PD, phénotype variable

- **Type A-** : Afrique noire, USA
- **Type méditerranéen**: plus fréquent,touche les caucasiens, phénotype plus grave, accidents hémolytiques plus sévères

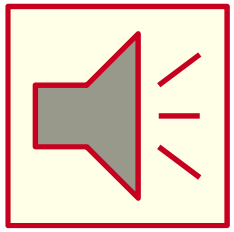
Tableau 1 Classification internationale des variants de la glucose-6-phosphate déshydrogénase (G6PD) en fonction de leur activité (selon [4]).

Classe I	Déficit enzymatique avec anémie hémolytique non sphérocytaire chronique
Classe II	Déficit enzymatique sévère avec activité enzymatique inférieure à 10 % de la normale
Classe III	Déficit enzymatique discret ou modéré avec activité enzymatique comprise entre 10 et 60 % de la normale
Classe IV	Activité comprise entre 60 et 150 % de la normale
Classe V	Activité accrue, supérieure à 150 % de la normale

Megarbane, Réanimation 2008, 17: 399-406

Déficit en G6PD et médicaments

Déficit en G6PD et médicaments



Liste incomplète Se réferer au site

Contre-indiquée

- Acide nalidixique
- Dapsone
- Nitrofurantoine
- Noramidopyrine / Métamizole sodique
- Rasburicase
- Sulfadiazine (voie orale)
- Sulfafurazol
- Sulfaguanidine
- Sulfaméthoxazole (voies orale et injectable)
- Sulfasalazine
- Triméthoprime (voies orale et injectable)

Déconseillée (sauf situation particulière) en raison de cas observés d'hémolyse aiguë

- Chloroquine
- Ciprofloxacine (voies orale et injectable)
- Dimercaprol
- Glibenclamide
- Lévofloxacine (voies orale et injectable)
- Norfloxacine (voie orale)
- Phytoménadione (vitamine K1)
- Spiramycine (voies orale et injectable)
- Sulfadiazine (voie locale)

Déconseillée (sauf situation particulière) en raison de l'appartenance à une classe pharmacologique à risque, ou d'un risque potentiel d'hémolyse

- Acide pipémidique
- Carbutamide
- Enoxacine
- Fluméquine
- Glibornuride
- Gliclazide
- Glimépiride
- Glipizide
- Hydroxychloroquine
- Loméfloxacine
- Moxifloxacine
- Ofloxacine (voies orale et injectable)
- Péfloxacine (voies orale et injectable)
- Phénazone (voie locale)
- Prilocaïne
- Quinine
- Sulfacétamide
- Sulfadoxine
- Sulfaméthizol

Déficit en G6PD, Diagnostic

- **Corps de Heinz** (non spécifique)
- **Dosage G6PD** (risque de faux négatif)
  - ***A coupler systématiquement avec le dosage de l'héxokinase***
  - ***Intérêt de l'enquête familiale dans les cas difficiles***
    - Dosage G6PD chez les parents et frères et soeurs
- Diagnostic **génétique moléculaire** généralement inutile

Déficit en pyruvate kinase

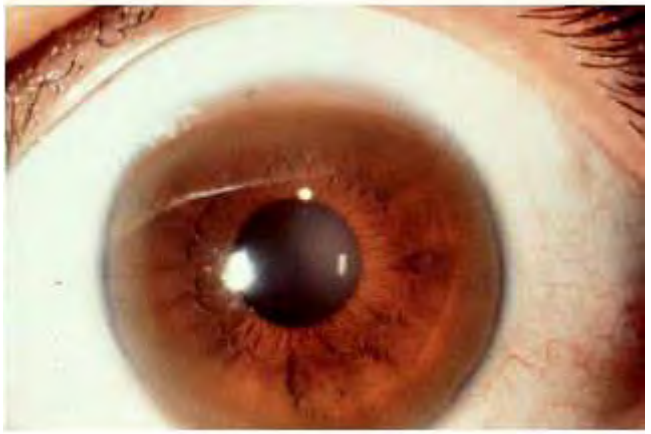
- Phénotype variable
- Facteur de protection contre le paludisme ?
- Répartition ubiquitaire (Europe du Nord, Chine…)
- **Hémolyse**, lithiase pigmentaire, érythrobastopénie, splénomégalie
- Dosage de PK
- Dg moléculaire: Non

- Femme, 23 ans, origine cambodgienne
- Adressée pour bilan d'une hémolyse
- Hb 7,5 g/dL, VGM 108 µL, réticulocytes: 154G/L
- ASAT 3 N, ALAT 4N
- TP: 51%, FV: 43%
- Echo abdo: splénomégalie 15 cm, dysmorphie hépatique, signes d'HTP
- Test de Coombs direct négatif,
- Absence de schizocytes
- Électrophorèse de l'Hb en attente

Maladie de Wilson

FOIE

Autosomique récessif
1/40 000 aux USA
Surcharge en cuivre
Dg génétique possible

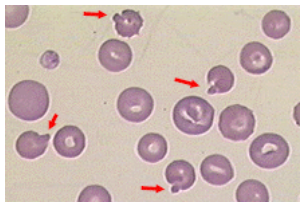


Nécrose
Relargage Cuivre
Stress oxydatif

Anneau de Kaser -Fleischer

Ponctuations basophiles
Corps de Heinz

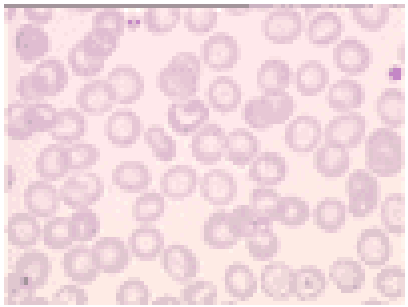
HEMOLYSE



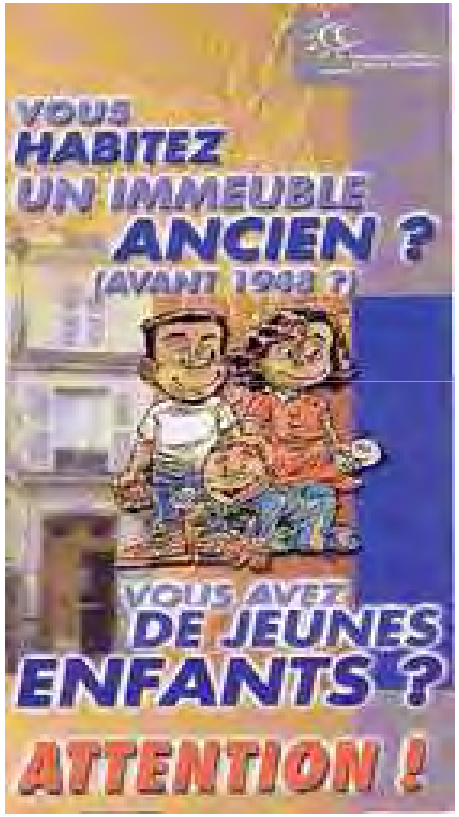
Hémolyses toxiques

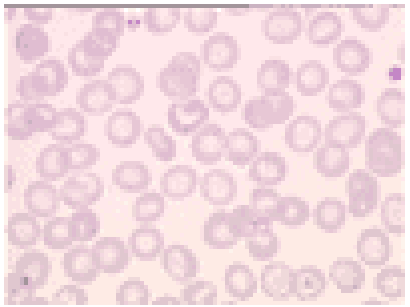
- Médicaments
  - ***Sulfones***
  - ***Ribavirine***
- Plomb
- Cuivre

Saturnisme



- Hémolyse
- Hématies ponctuées
- Douleurs abdominales
- HTA
- Pigmentation des gencives
- Plombémie et plomburie ↗↗↗





- **Hématies ponctuées** : hématies (en réalité réticulocytes) contenant de nombreuses petites ponctuations sombres, basophiles (témoin d'une anomalie de synthèse de l'hémoglobine)
  - *Thalassémies*
  - *Anémies sidéroblastiques (secondaires (Pb) et primitives)*
  - *Splénomégalie myéloïde*
  - *Grandes dysérythropoïèses*
  - *Chez le nouveau-né (ponctuations fines)*

Anémie hémolytique

Frottis sanguin + test de Coombs direct

- Anomalies morphos des GR Coombs -
  - Anémies corpusculaires (anomalie d'Hb ou Membrane)
    - Microspherocytose Elliptocytose Drépanocytose..
      - Test de résistance osm. Ektacytométrie Electrophorèse Hb.
- Schizocytes* ++ Coombs -
  - MAT (PTT, SHU, HELLP..) *Attention aux « pseudo-MAT »*
- Frottis Nl (ou corps de Heinz ± ponct. basos… Coombs -
  - Déficit G6PD, PK
    - NON
      - AHAI à Coombs -
      - HPN CD55/59
      - Intox. Pb Wilson
      - Hb instable
- Frottis Nl ou sphéro. Coombs +
  - **AHAI**

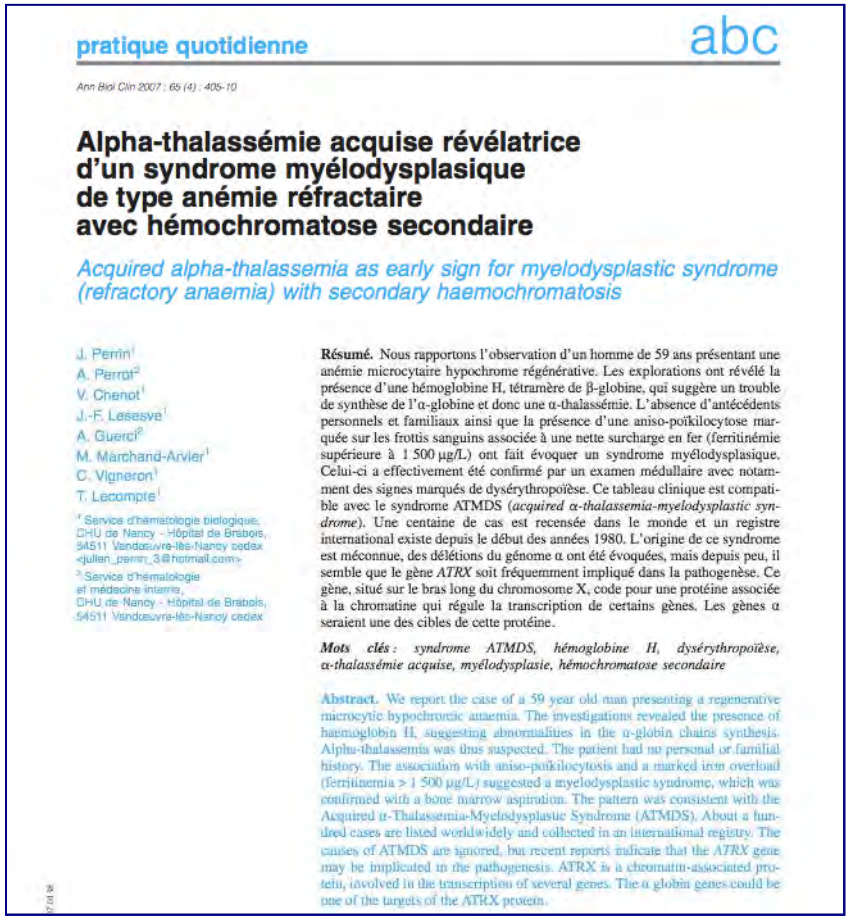
Que faire quand on a rien trouvé ?

- AHAI à Coombs négatif ?
- Désinsertion de valve mécanique ?
- Hb instable ?
- **FAIRE UN MYELOGRAMME**

Sd «ATMDS »

Acquired α-thalassemia myelodysplastic syndrome

- *α-thalassémie acquise*
- *Déletion d'un ou deux gènes α*
- *Hémoglobine H*
- *Anémie microcytaire hypochrome*
- *Surcharge martiale*
- *HPLC, Electrophorèse Hb (acétate cellulose, isoélectro-focalisation)*
- *MDS, SMP, etc…*



pratique quotidienne abc

Ann Biol Clin 2007 ; 65 (4) : 405-10

Alpha-thalassémie acquise révélatrice d'un syndrome myélodysplasique de type anémie réfractaire avec hémochromatose secondaire

Acquired alpha-thalassemia as early sign for myelodysplastic syndrome (refractory anaemia) with secondary haemochromatosis

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Résumé. Nous rapportons l'observation d'un homme de 59 ans présentant une anémie microcytaire hypochrome régénérative. Les explorations ont révélé la présence d'une hémoglobine H, tétramère de β-globine, qui suggère un trouble de synthèse de l'α-globine et donc une α-thalassémie. L'absence d'antécédents personnels et familiaux ainsi que la présence d'une aniso-poïkilocytose marquée sur les frottis sanguins associée à une nette surcharge en fer (ferritinémie supérieure à 1 500 µg/L) ont fait évoquer un syndrome myélodysplasique. Celui-ci a effectivement été confirmé par un examen médullaire avec notamment des signes marqués de dysérythropoïèse. Ce tableau clinique est compatible avec le syndrome ATMDS (*acquired α-thalassemia-myelodysplastic syndrome*). Une centaine de cas est recensée dans le monde et un registre international existe depuis le début des années 1980. L'origine de ce syndrome est méconnue, des délétions du génome α ont été évoquées, mais depuis peu, il semble que le gène *ATRX* soit fréquemment impliqué dans la pathogenèse. Ce gène, situé sur le bras long du chromosome X, code pour une protéine associée à la chromatine qui régule la transcription de certains gènes. Les gènes α seraient une des cibles de cette protéine.

Mots clés : *syndrome ATMDS, hémoglobine H, dysérythropoïèse, α-thalassémie acquise, myélodysplasie, hémochromatose secondaire*

Abstract. We report the case of a 59 year old man presenting a regenerative microcytic hypochromic anaemia. The investigations revealed the presence of haemoglobin H, suggesting abnormalities in the α-globin chains synthesis. Alpha-thalassemia was thus suspected. The patient had no personal or familial history. The association with aniso-poïkilocytosis and a marked iron overload (ferritinemia > 1 500 µg/L) suggested a myelodysplastic syndrome, which was confirmed with a bone marrow aspiration. The pattern was consistent with the Acquired α-Thalassemia-Myelodysplastic Syndrome (ATMDS). About a hundred cases are listed worldwidely and collected in an international registry. The causes of ATMDS are ignored, but recent reports indicate that the *ATRX* gene may be implicated in the pathogenesis. ATRX is a chromatin-associated protein, involved in the transcription of several genes. The α globin genes could be one of the targets of the ATRX protein.

Perrin et al, Ann Biol Clin 2007; 65: 405-10

Presse Med. 2011; □□: □□□

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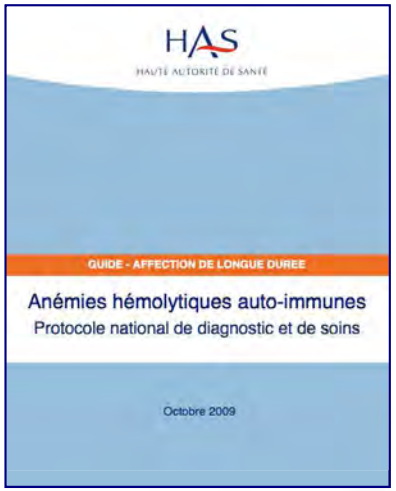
Mise au point



Anémie hémolytique chez l'adulte : principales causes et démarche diagnostique

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