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### CLINICAL SIGNIFICANCE OF PNH CLONES IN 3085 PATIENTS WITH CYTOPENIA: A LARGE SINGLE-CENTER EXPERIENCE

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#### INTRODUCTION

PNH is a rare acquired clonal disorder of hematopoietic stem cell.  
**PNH cells** are deficient in GPI anchored proteins and are damaged by aberrant complement activation.  
**RBC-PNH cells** undergo chronic intravascular hemolysis leading to anaemia, hemoglobinuria, thrombosis and acute/chronic end-organ damage

**Three subgroups have been identified :**  
 classic PNH  
 AA/MDS PNH  
 subclinical PNH

PNH survival may be over 10 years  
 major cause of mortality and morbidity is **thrombosis**

#### AIM

To evaluate the prevalence of PNH clone in 3085 patients with cytopenia tested at a single tertiary center, and to assess their relationship with disease severity and outcome.

#### RESULTS

3085 patients tested since 1998  
 389 before FLAER era

PNH+ 20% MDS, 61% AA, 81% MDS/AA overlap  
 17% MPN, 12.2% acute leukaemia, **7% isolated cytopenia**, 5% isolated thrombosis.

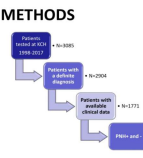
Positive patients were younger  
 With > frequency of **Anaemia, thrombocytopenia and increased LDH**

PNH+MDS and AA were significantly more **thrombocytopenic** and had **higher LDH** than PNH-cases

	PNH neg	PNH pos	p
N of pts tested	2311 (75)	774 (25)	
Clinical data available	2160/2311 (93.4)	744/774 (96)	
Males	1168(54)	388 (52)	0.13
Females	992 (46)	367 (48)	0.13
median age years	55 (0-91)	47 (1-89)	<0.0001
N=1027	N=744		
Anemia (Hb<10) N(%)	409 (40)	351 (47)	0.017
Thrombocytopenia (PLT<100)N(%)	463 (45)	423 (57)	<0.0001
Neutropenia (ANC<1500) (N%)	478 (46.5)	342 (46)	0.7
Pancytopenia N(%)	160 (16)	183 (24.5)	<0.0001
Median LDH U/L	212 (92-1520)	245 (70-4614)	<0.0001

#### METHODS

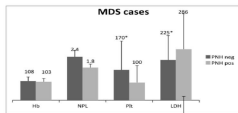
We collected clinical (diagnosis, stage, therapy, complications and outcome) and laboratory features (complete blood counts, LDH, PNH clone) of 3085 patients tested from March 1998 till October 2017.



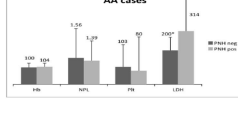
#### CONCLUSIONS

FLAER technique can detect very small PNH clones (<1%) whose clinical significance is controversial. Even the presence of small clones correlates with lower blood counts, increased LDH, and occurrence of thrombosis. Prevalence of PNH clones is high in patients with AA and MDS and carries prognostic significance. PNH+AA and MDS are younger, more frequently receive IST, and show better survival

#### MDS cases

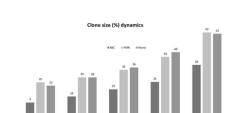


#### AA cases



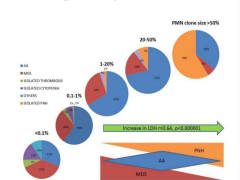
**PNH+MDS** received >IST and <Chemo or AZA; showed <MDS progression/AML evolution, <death, but >thrombosis

**PNH+AA** received >IST and showed <MDS progression and <deaths  
**Mean clone size (N=230) progressively increased** along time, particularly in haemolytic PNH cases treated with eculizumab.

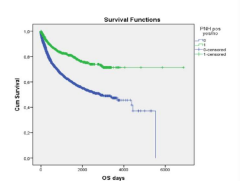


#### MDS displayed smaller clones than AA and haemolytic PNH.

PNH clone size positively correlated with LDH levels (p<0.0001).



**PNH+ patients showed longer OS from 1st test (p<0.0001)**  
 The statistical significance was retained even considering MDS and AA separately





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Abstract

**Abstract:** PF304

**Type:** Poster Presentation

**Presentation during EHA23:** On Friday, June 15, 2018 from 17:30 - 19:00

**Location:** Poster area

## Background

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare clonal disorder due to GPI anchored proteins deficiency on blood cells surface, resulting in complement activation and chronic intravascular hemolysis. Along with classic one, PNH in the setting of bone marrow disorder [aplastic anemia (AA)/myelodysplastic syndrome (MDS)], and subclinical PNH, with a small PNH population and no evidence of hemolysis, have been described. The prevalence and clinical significance of PNH clones, especially small ones, detected by high sensitive FLAER are still under debate.

## Aims

To evaluate the prevalence of PNH clone in 3085 patients with cytopenia tested at a single tertiary center, and to assess their relationship with disease severity and outcome.

## Methods

We collected clinical (diagnosis, stage, therapy, complications and outcome) and laboratory features (complete blood counts, LDH, PNH clone) of 3085 patients tested from March 1998 till October 2017.

## Results

Main baseline clinical and laboratory characteristics of patients, divided according to presence or absence of PNH clones, are shown in table 1. PNH clone (PNH+) was found in 774 cases (25%), mostly AA (44%), MDS (24%), and florid hemolytic PNH (13%). Clone size, evaluated on granulocyte in 468 cases, was <1% in 224, 1-50% in 120, and >50% in 124, and correlated with LDH levels ( $p<0.0001$ ). Considering diagnosis, PNH+ MDS displayed smaller clones compared to AA and haemolytic PNH ones (60% of cases with PNH clone size >50%). Serial PNH clone evaluation ( $n=230$ ), showed mean clone size increase along time, particularly in haemolytic PNH cases treated with eculizumab. Among PNH- cases, the most frequent reason for testing were MDS (32%), idiopathic cytopenia (23.7%), and isolated thrombosis (13%). PNH+ cases were younger ( $p<0.0001$ ), more frequently anaemic ( $p=0.01$ ), thrombocytopenic ( $p=0.0003$ ), or pancytopenic ( $p<0.0001$ ), with higher LDH ( $p<0.0001$ ). PNH+ patients also showed longer OS from first test [mean 14.24+0.35 years (95%CI 13.56-14.93) versus 8.16+0.26 years (7.64-8.68),  $p<0.0001$ ]. PNH+ MDS patients ( $N=176$ , 20.3%) were significantly younger, more hypoplastic ( $p<0.001$ ), and less frequently showed excess of blast ( $p=0.01$ ); they also showed deeper cytopenias ( $p=0.04$  for Hb, and  $p<0.0001$  for PLT), and had higher LDH levels ( $p<0.0001$ ). Moreover, they had more frequently received cyclosporine and ATG ( $p=0.0001$ ), less frequently chemotherapy or azacytidine ( $p<0.0001$  and  $p=0.002$ ), and 7 cases had been treated with eculizumab. PNH+ MDS showed lower rate of higher risk progression ( $p=0.003$ ), AML evolution ( $p=0.01$ ), and death ( $p<0.0001$ ), but had higher incidence of thrombotic events ( $p=0.05$ ). Survival analysis also showed a longer OS for PNH+ MDS [mean 11.9+0.7 years (10.5-13.3) vs 7.3+0.3 (6.6-7.9),  $p<0.0001$ ] compared to PNH- ones. PNH+ AA (61%) showed deeper thrombocytopenia ( $p<0.0001$ ), higher reticulocyte counts ( $p=0.0004$ ) and LDH values ( $p<0.0001$ ). PNH+ AA were more frequently treated ( $p<0.0001$ ), and showed lower MDS progression and deaths ( $p=0.01$  and  $p<0.0001$ ), and longer OS [mean 15.8+0.43 years (14.9-16.7) vs 6.5+0.35 (5.8-7.21),  $p<0.0001$ ].

**Table 1 Patients screened for PNH clones at our Institution**

N 3085	PNH neg	PNH pos
Study period	Mar 1998 to Oct 2017	
Number of patients, N (%)	2311 (75)	774 (25)
Male/Female ratio	1.17	1.05
median age years (range)	55 (0-91)	47 (1-89)*
	<b>N=2160</b>	<b>N=744</b>
MDS N(%)	693 (32)	176 (23.6)*
AA N(%)	204 (9.4)	327 (43.9)*
MDS/AA N(%)	5 (0.2)	22 (2.9)*
Acute leukemia N(%)	209 (9.6)	29 (3.9)*
Haemolytic PNH N(%)	0 (0)	97 (13)
MPN N(%)	76 (3.5)	16 (2.15)
MDS/MPN N(%)	92 (4.2)	9 (1.2)*
Isolated cytopenia N(%)	512 (23.7)	39 (5.2)*
Isolated thrombosis N(%)	284 (13)	17 (2.3)*
Other reason N(%)	85 (3.9)	12 (1.6)*
Thrombosis occurrence N(%)	370 (17.12)	96 (12.9)
Death N(%)	725 (33.6)	141 (18.9)*
Lost to follow-up N(%)	146 (6.75)	75 (10)
Haematological parameters	<b>N=1027</b>	<b>N=744</b>
Hb<100 g/L, N(%)	409 (40)	351 (47)**
PLT<100x10 <sup>3</sup> /mmc, N(%)	463 (45)	423 (57)*
ANC<1.5x10 <sup>3</sup> /mmc, N(%)	478 (46.5)	342 (46)
Pancytopenia N(%)	160 (16)	183 (24.5)*
Median LDH U/L (range)	212 (92-1520)	245 (70-4614)*

\* $p\leq 0.0001$ , \*\* $p=0.01$

## Conclusion

Prevalence of PNH clones of any size is high in patients with bone marrow failure and carries prognostic significance. In this largest reported retrospective series, even the presence of small clones correlates with lower blood counts, increased LDH, and occurrence of thrombosis. Finally, PNH positivity seems to be more frequent in patients of younger age and to predict a better survival

Session topic: 12. Bone marrow failure syndromes incl. PNH - Clinical

Keyword(s): Aplastic anemia, Myelodysplasia, Paroxysmal nocturnal hemoglobinuria (PNH)

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