APLASIE MEDULLAIRE
centre de référence

Manifestations rares de la Maladie de Fanconi

MaRIH
Filière de santé Maladies Rares ImmunoHématologiques

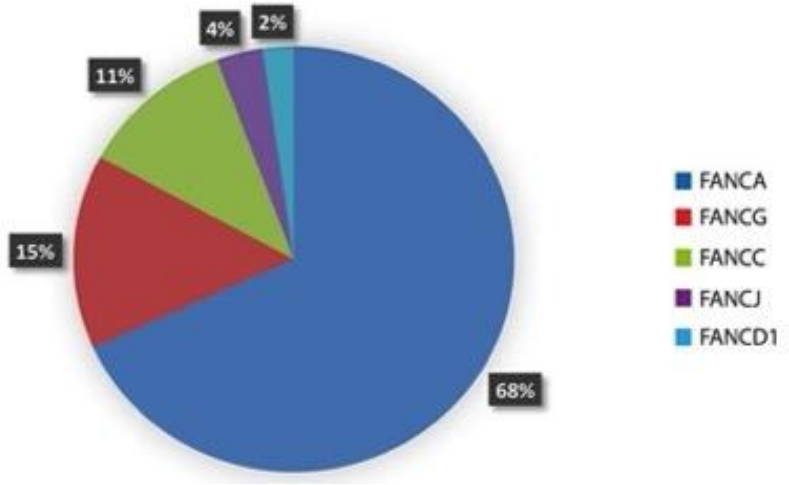
Journée annuelle CRMR CeRAMIC, 3 Octobre 2025

centre de référence
maladies rares

Manifestations Neurologiques

Anomaly	N=111
Any anomaly	100 (90.1%)
Café-au-lait spots	58 (52.3%)
Renal structure	44 (39.6%)
CNS structure	21 (18.9%)
Hearing loss	20 (18%)
Congenital heart disease	18 (16.2%)
Male genitourinary	18 (16.2%)
Radial ray	18 (16.2%)
Gastrointestinal structure	9 (8.1%)
Spine	6 (5.4%)
Cleft lip/palate	2 (1.8%)

Anomalies as reported in patient charts.



CNS abn >> in FA downstream genes / FA core (p:0.005)

Steinberg-Shemer et al, Haematologica 2020

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Spine	6 (5.4%)
Cleft lip/palate	2 (1.8%)

Anomalies as reported in patient charts.

Présentes dès la naissance, retentissement variable

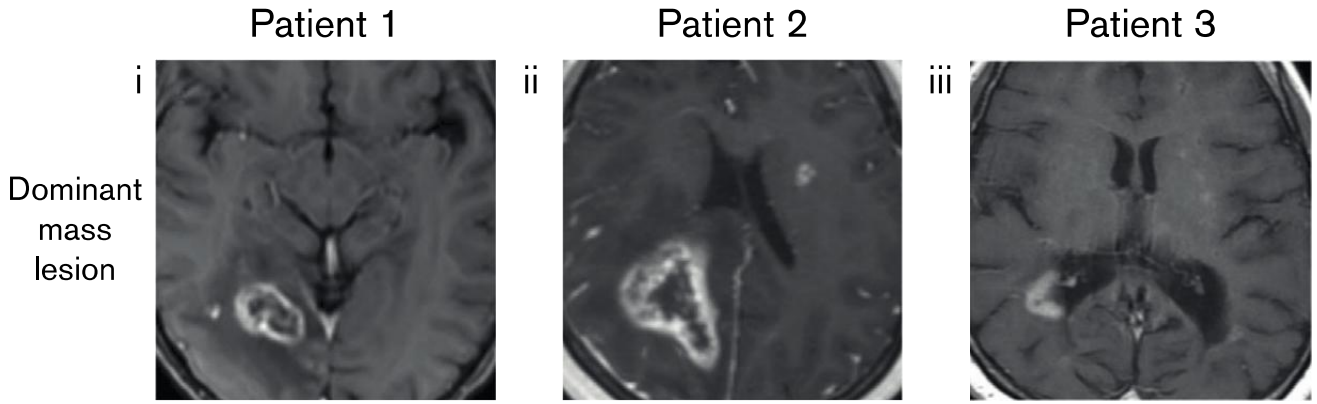
- Small pituitary gland
- Chiari I malformations
- Ectopic neurohypophysis
- Adenohypophysis hypoplasia
- Platy- basia

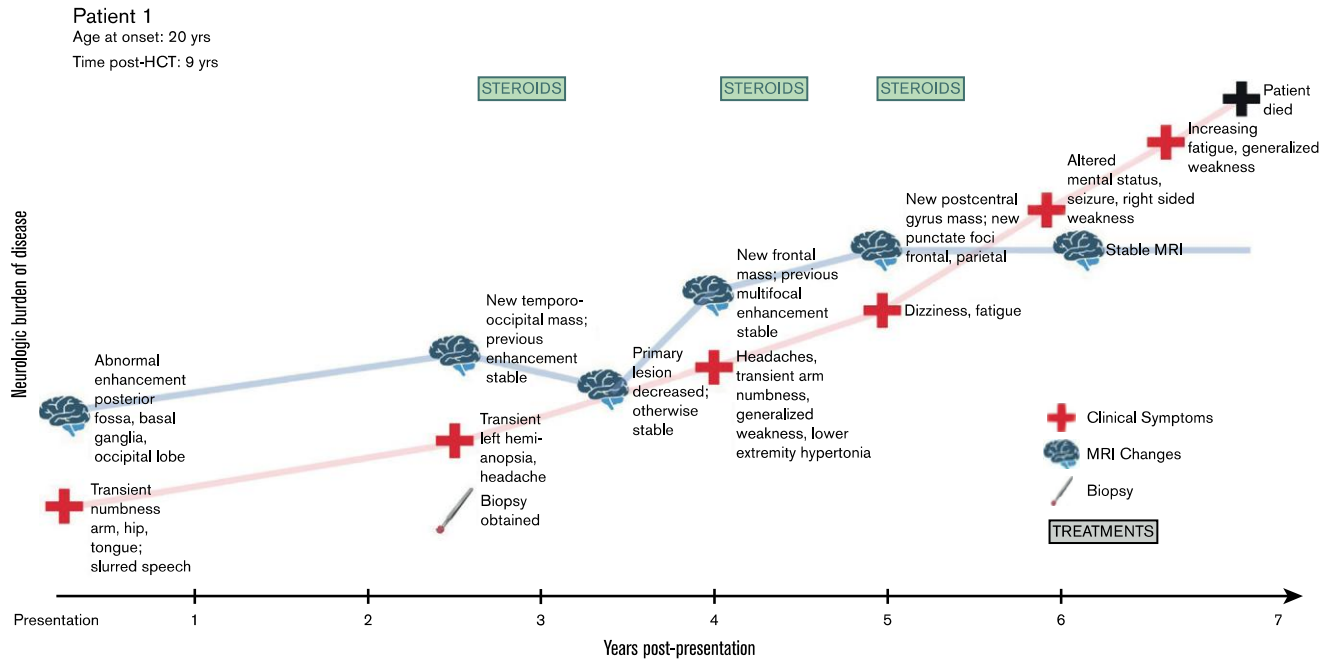
Steinberg-Shemer et al, Haematologica 2020

Stivaros et al, Br Jr of Radiology 2015

Fanconi anemia neuroinflammatory syndrome: brain lesions and neurologic injury in Fanconi anemia

Bartlett et al Blood advances 2024





FANS

Fanconi anemia neuroinflammatory syndrome: brain lesions and neurologic injury in Fanconi anemia

Bartlett et al Blood advances 2024

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Age, y	27	24	20	21	29	20	18	27	17
Age at FANS presentation, y	20	19	13	11	22	17	17	24	16
Sex	Female	Male	Male	Female	Female	Female	Male	Male	Male
FA complementation group	FANCL	FANCJ	FANCF	FANCD2	FANCC	Unknown	Unknown	FANCD3	Unknown
HCT, Y/N	Y	N	Y	Y	Y	Y	Y	Y	Y
Age at HCT, y	11	N/A	5	8	9	4	9	7	7
Transplant type	MUD	N/A	MUD	MSD	MSCBT	MSD	MUCBT	MUD	MUD
Preparative regimen	Flu/Cy/ATG	N/A	Flu/Cy/ATG/TBI	Flu/Cy/ATG	Cy/TBI	Bu/Flu/ATG	Flu/Cy/ATG/TBI	Flu/Cy/ATG/TBI	Bu/Flu/Cy/ATG
GVHD prophylaxis	T-cell depletion; CsA, MP	N/A	T-cell depletion; CsA, MP	CsA	None	T-cell depletion; OKT3	CsA, MP	T-cell depletion; CsA	T-cell depletion; CsA
Post-HCT complications	Skin GVHD, CKD, cholestasis, AVN	N/A	Ocular GVHD, hepatic dysfunction, and hypothyroidism	Hepatic dysfunction and hypothyroidism	Hepatic dysfunction, hypothyroidism, and feeding difficulties	Ocular GVHD and skin GVHD	Hepatic dysfunction, hypothyroidism, and hypertension	Skin GVHD and gastrointestinal GVHD	CKD, cholestasis, and feeding difficulties
Onset of FANS after HCT, y	9	N/A	8	3	13	13	8	17	9
Neurologic symptoms at presentation	Transient right sided numbness and slurred speech	Transient hemiplegia	Visual defect and slurred speech	Right hand weakness	Vertigo	Headache and neck pain	Headaches, blurry vision, and fatigue	Spastic paraparesis and progressive weakness	Papilledema (incidental finding)
Evolving neurologic symptoms	Unilateral hemianopsia, lower extremity hypertonia/ hyperreflexia, and numbness episodes (arm, hip, and tongue)	Unilateral hemianopsia, hemiparesis, seizures, and intermittent explosive disorder	Cranial nerve palsies, paresthesias, seizures, ataxia, and depression	Intermittent hemiparesis, paraparesis, and left upper quadrantanopia	Vertigo, tics, tongue fasciculations, and myoclonic jerks	Upper and lower extremity paresthesias, leg pain, and dizziness	Seizures, ataxia, and less verbal	Headaches, dysphagia, dysarthria, incontinence, altered mental status, facial droop, and hypophonia	Seizure

11 - 24 ans

Fanconi anemia neuroinflammatory syndrome: brain lesions and neurologic injury in Fanconi anemia

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Sex	Female	Male	Male	Female	Female	Female	Male	Male	Male
FA complementation group	FANCL	FANCJ	FANCF	FANCD2	FANCC	Unknown	Unknown	FANCD3	Unknown
HCT, Y/N	Y	N	Y	Y	Y	Y	Y	Y	Y
Age at HCT, y	11	N/A	5	8	9	4	9	7	7
Transplant type	MUD	N/A	MUD	MSD	MSCBT	MSD	MUCBT	MUD	MUD
Preparative regimen	Flu/Cy/ATG	N/A	Flu/Cy/ATG/TBI	Flu/Cy/ATG	Cy/TBI	Bu/Flu/ATG	Flu/Cy/ATG/TBI	Flu/Cy/ATG/TBI	Bu/Flu/Cy/ATG
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variable

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FA complementation group	FANCL	FANCJ	FANCF	FANCD2	FANCC	Unknown	Unknown	FANCD3	Unknown
HCT, Y/N	Y	N	Y	Y	Y	Y	Y	Y	Y
Age at HCT, y	11	N/A	5	8	9	4	9	7	7
Transplant type	MUD	N/A	MUD	MSD	MSCBT	MSD	MUCBT	MUD	MUD
Preparative regimen	Flu/Cy/ATG	N/A	Flu/Cy/ATG/TBI	Flu/Cy/ATG	Cy/TBI	Bu/Flu/ATG	Flu/Cy/ATG/TBI	Flu/Cy/ATG/TBI	Bu/Flu/Cy/ATG
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7/8 HSCT

4/8 GvHD tardif

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Sex	Female	Male	Male	Female	Female	Female	Male	Male	Male
FA complementation group	FANCL	FANCJ	FANCF	FANCD2	FANCC	Unknown	Unknown	FANCD3	Unknown
HCT, Y/N	Y	N	Y	Y	Y	Y	Y	Y	Y
Age at HCT, y	11	N/A	5	8	9	4	9	7	7
Transplant type	MUD	N/A	MUD	MSD	MSCBT	MSD	MUCBT	MUD	MUD
Preparative regimen	Flu/Cy/ATG	N/A	Flu/Cy/ATG/TBI	Flu/Cy/ATG	Cy/TBI	Bu/Flu/ATG	Flu/Cy/ATG/TBI	Flu/Cy/ATG/TBI	Bu/Flu/Cy/ATG
GVHD prophylaxis	T-cell depletion; CsA, MP	N/A	T-cell depletion; CsA, MP	CsA	None	T-cell depletion; OKT3	CsA, MP	T-cell depletion; CsA	T-cell depletion; CsA
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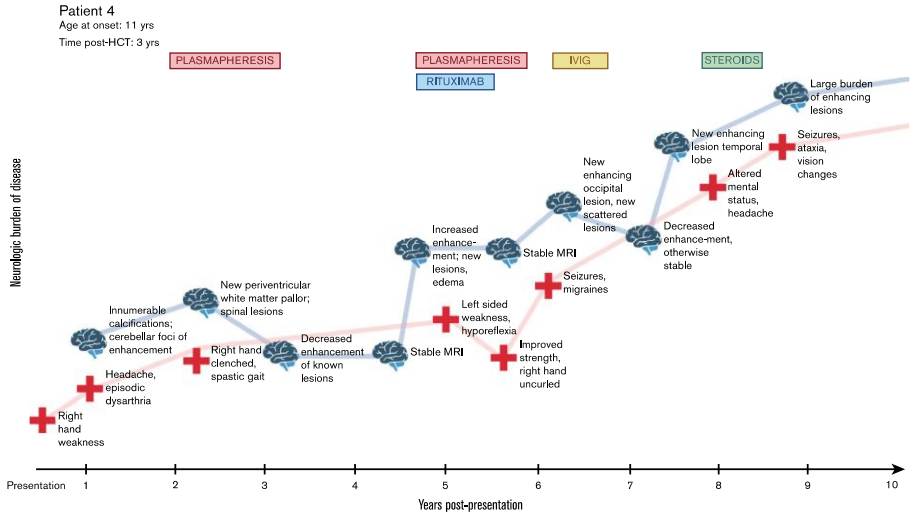
Ttt	Steroids	Steroids Sirolimus Anakinra	Ciclosporin Steroids	Plasmapheresis Rituximab IgIv Steroids	None	None	None	Steroids	Steroids
Duration of neurologic involvement, y	7	5	7	10	10	4	2	2	1
Cause of death	Renal failure	N/A	N/A	N/A	N/A	N/A	CNS nocardiosis	N/A	N/A



Fanconi anemia neuroinflammatory syndrome: brain lesions and neurologic injury in Fanconi anemia

Bartlett et al Blood advances 2024

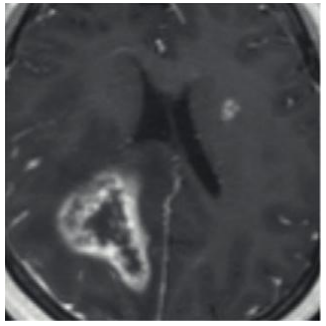
blood advances

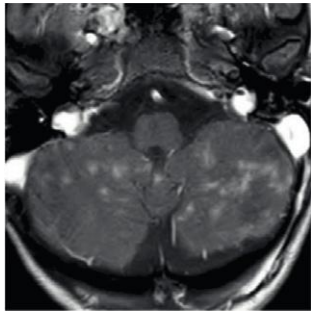
Caractéristiques IRM

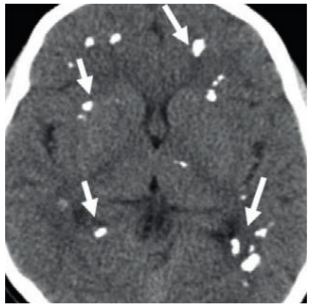
- Une lésion dominante avec rehaussement en anneau
- Petits foyers prise de contraste dispersés
- Calcifications

- Prédominent lobe pariétal l
- Œdème avec effet de masse fréquent

- Prise de contraste moelle épinière 50%



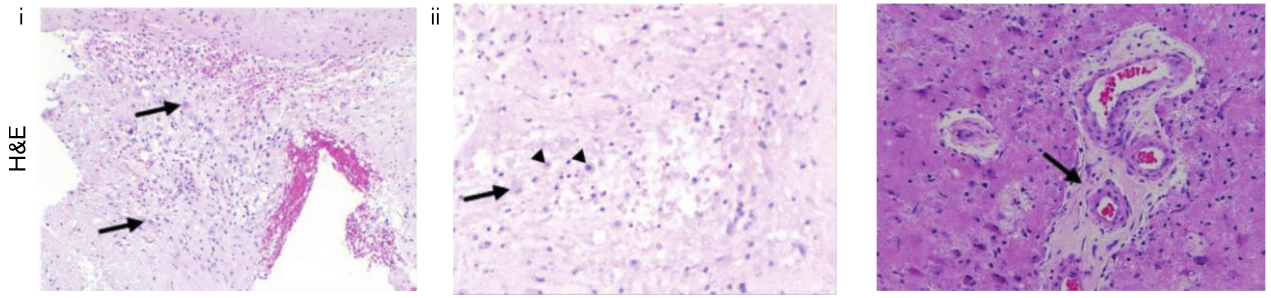




Histologie

Processus nécrotique inflammatoire :

- Prolifération gliale réactionnelle & macrophages
- Zones nécroses parfois calcifiées zones
- Vascularisation, cellules endothéliales hypertrophiées
- Plages de hyalinisation focales
- Pas de lésions néoplasiques



→ nécrose

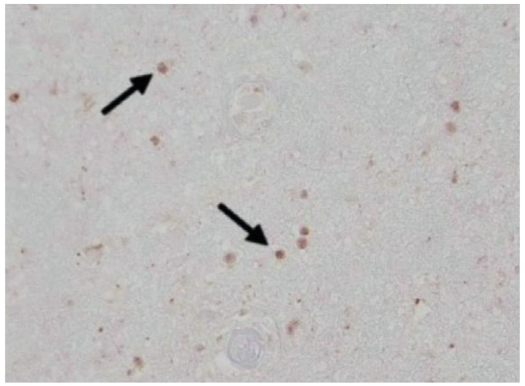
► macrophages

→ Hyperplasie Vx, hyalinisation

FANS, hypothèses physiopathologiques

- Infectieuse ?

  JC virus



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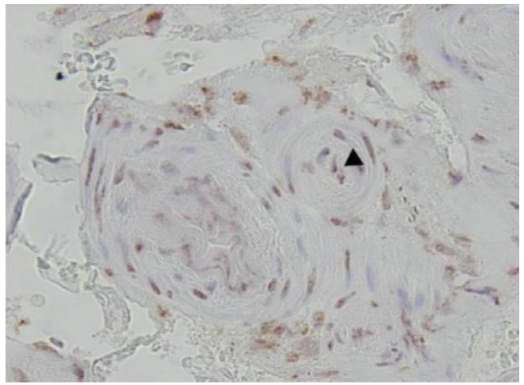


IHC
Sv 40

FANS Pt 2 LEMP

- Manifestation auto-inflammatoire (interferonopathies):
  - Cliniques : anomalies CV, hémiparésies, déficit moteur, hémianopsies et aphasies
  - Lésions histologiques proches : nécroses, vascularisation, cellules endothéliales hypertrophiées, hyalinisation focales

➡ **Manifestations inflammatoires (déficit de réparation ?)**
Favorisées par l'allogreffe
Facteur déclenchant infectieux ?

FANS, hypothèses physiopathologiques

FANCC deficiency mediates microglial pyroptosis and secondary neuronal apoptosis in spinal cord contusion

Xia *et al. Cell & Bioscience* (2022) 12:82

Mingjie Xia[1†], Xinyu Li[2†], Suhui Ye[3,4†], Qinyang Zhang[5,6], Tianyu Zhao[5,6], Rulin Li[5,6], Yanan Zhang[5,6], Minghan Xian[5,6], Tianqi Li[5,6], Haijun Li[6], Xin Hong[3,4], Shengnai Zheng[1*], Zhanyang Qian[3,4*] and Lei Yang[6,7*]

Results: Overexpression of FANCC suppressed microglial pyroptosis via inhibiting p38/NLRP3 expression, which in turn reduced neuronal apoptosis. By contrast, knockdown of FANCC increased the degree of neuronal apoptosis by aggravating microglial pyroptosis. Besides, increased glial scar formation, severe myelin sheath destruction and poor axon outgrowth were observed in the mice transfected with short hairpin RNA of FANCC post SCI, which caused reduced locomotor function recovery.

Conclusions: Taken together, a previously unknown role of FANCC was identified in SCI, where its deficiency led to microglia pyroptosis, neuronal apoptosis and neurological damage. Mechanistically, FANCC mediated microglia pyroptosis and the inflammatory response via regulating the p38/NLRP3 pathway.

FANS, hypothèses physiopathologiques

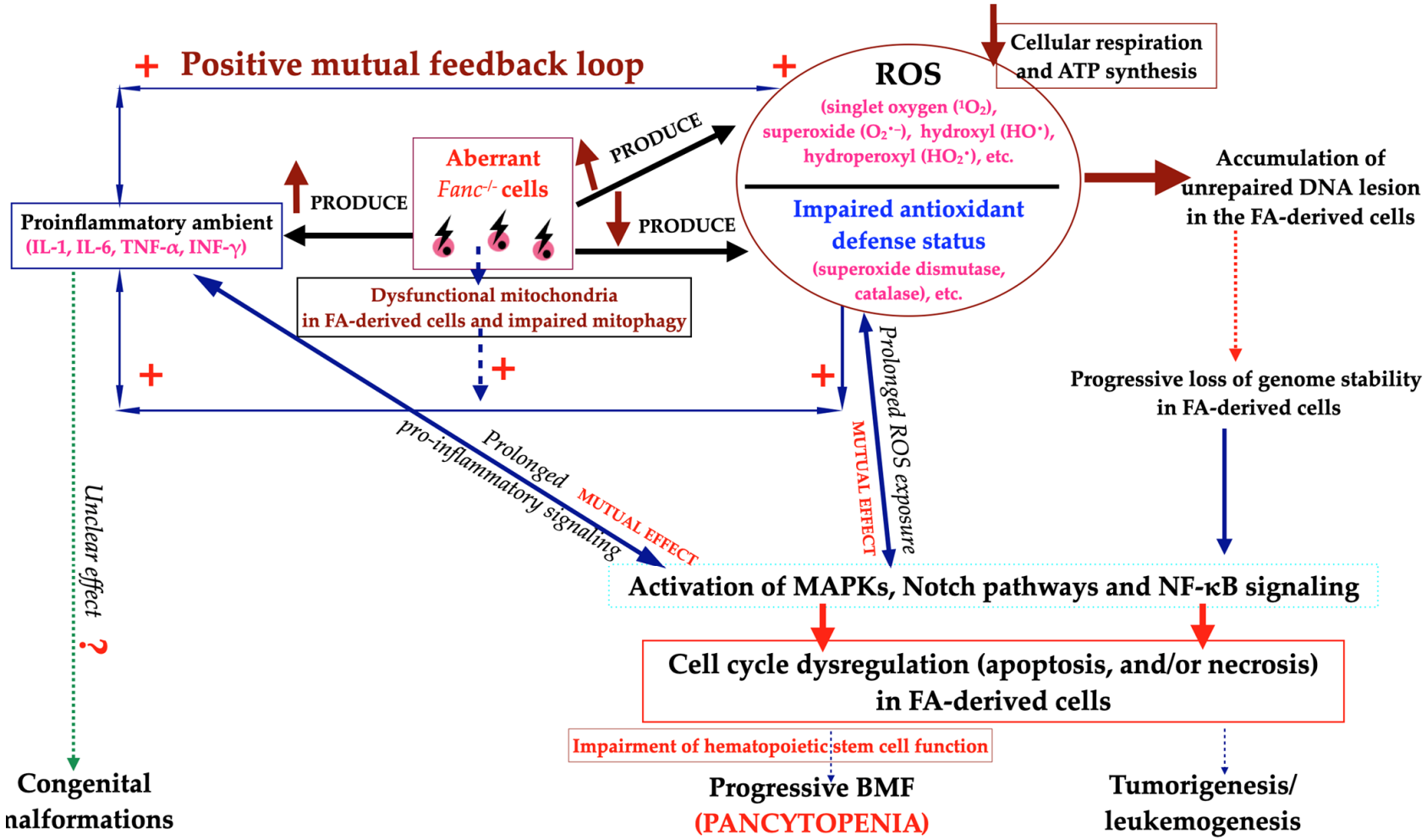


Figure 4. Schematic representation of how biallelic pathogenic variants in *FANC* (*Fanc*$^{-/-}$) genes trigger a vicious circle between proinflammatory cytokines, oxidative genotoxic stress and MAPK, Notch as well as NF-κB signaling pathways.

Repczynska et al. Int Jour Mol Science, 2024

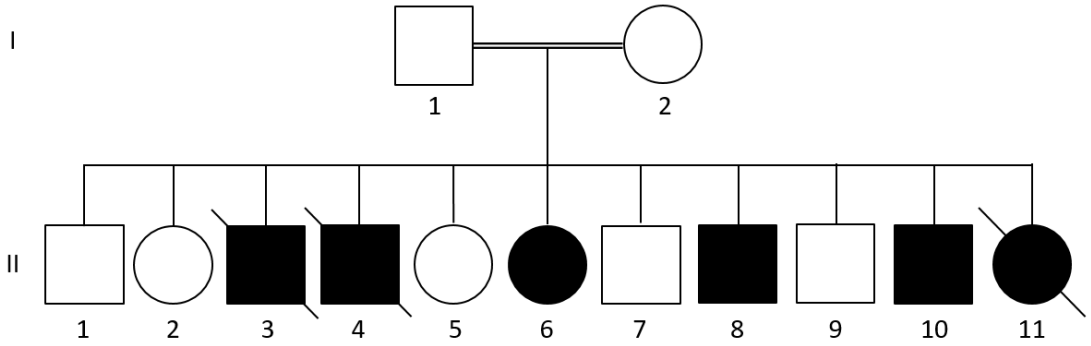
FANS, prévalence

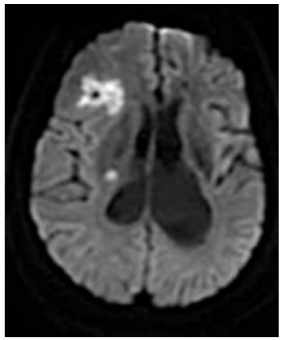
- **Bartlett et al Blood advances 2024**
  - Revue rétrospectives imageries (132 IRM et 90 scanners cérébraux) 34 patients (âge médian 11 ans, 1-31)
  - 0 autre cas

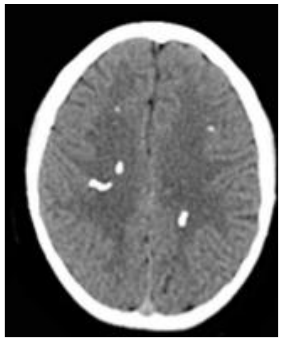
- **Avril 2024, Ramachandran et al, Neurology**
  - 16 patients (6 US & 10 EU)
  - Aggravation neurologique progressive avec épisodes aigus
  - Hemiparésie, spastiicté, sd cerebelleux, crises comitiales
  - Vasculopathie retinienne 70% cas angiographie
  - IRM :
    - Lésions avec prise de contraste annulaire predo au cervelet, accumulation progressive
    - Aspect pseudo-tumoral
  - Histologie similaire
  - Echec des traitements IS

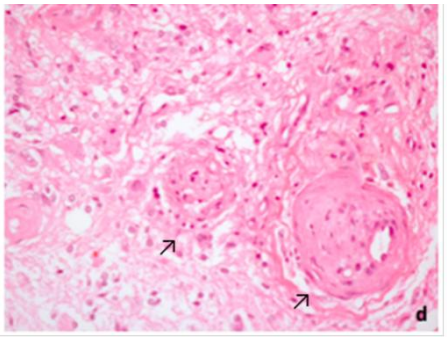
FANS, prévalence

- **2024, Cousyn et al, J Neuro Neurosurg psychatry**









- Facies caracteristique
- Taches Café-au-lait 3/6
- Syndactylie and microcephalie 1/6
- Thrombopenie 4/6 et anémie 2/6
- Test de cassure pathologique & profil FA core / FANCD2

= > mutation HMZ FANCL exome

4/6 manifestations neurologiques 11-14 ans:

- **Hémiparésie, aphasie and comitialité**
- **Hypertension intracérébrale**
- **Lésions IRM/histo similaires**
- **Amélioration sous corticoïdes chez 2**

➡ Rôle du génotype ? FANCL 0,2-0,4% des FA

FANS, implications en termes de prise en charge

- **Complication rare**
- **Dépistage par suivi IRM semble non nécessaire**
- **Etude rétrospective de la cohorte française :**
  - Prévalence ?
  - Rôle de la greffe ?
  - Facteurs de risques ? Génotype ?

- **Centralisation de la prise en charge nouveaux cas ?**
  - Biopsie : congélation ? Autres explorations ?
  - Prise en charge thérapeutique homogène

Manifestations Pulmonaires

- Anomalies pulmonaires peu décrites
- Questions régulières AFMF sur des manifestations rapportées par les patients
- Quelles sont les données de la littérature ?

Lung Function in Patients With Fanconi Anemia

S. J. Rose[1], A. Nelson[2], K. Myers[2], C. Towe[1]; [1]Pediatric Pulmonology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States, [2]Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States.

Pulmonary Function Test	Pre- HSCT (n=52)	Post- HSCT (n=81)
Forced Vital Capacity (FVC)	-0.85 ± 1.41 90.6% ± 15.8%	-1.26 ± 1.21 86.10% ± 13.41%
Forced Expiratory Volume in 1 second (FEV1)	-1.44 ± 1.18 82% ± 14.3%	-1.67 ± 0.97 79.94% ± 11.89%
Total Lung Capacity (TLC)	-1.01 ± 1.16 82.27% ± 14.44%	-1.44 ± 1.08 82.14% ± 13.16%
Diffusion Capacity for Carbon Monoxide (DLCO)	-1.34 ± 1.20 82.4% ± 15.7%	-1.50 ± 1.05 80.15% ± 13%
Results expressed as mean z score (above) and mean percent predicted (below) ± standard deviation		

- **Pre HSCT:**

Lower FVC, FEV1, TLC, and DLCO

No impact of age, BMI, or race

- **Post HSCT:**

Decrease FVC, FEV1, TLC, and DLCO

No impact of radiation exposure, race, BMI, or age.

Lower FVC and FEV1 if BMI <10th

- **Post vs Pre HSCT (n=31):**

Decrease FVC, FEV1, TLC, and DLCO

FEV1 normalized at 1 y

Late Effects Following Hematopoietic Stem Cell Transplantation Among Childhood Transplant Survivors with Fanconi Anemia

Çocuklukta Nakil Yapılan Fanconi Anemili Hastalarda Hematopoietik Kök Hücre Nakli Sonrası Geç Dönem Etkiler

36 patients greffés (médiane 6 ans, FU médian 9 ans)

Age at last follow-up, years	
Median (range)	17.5 (6.1-36)
Patients ≥18 years at the last follow-up	15 (42)
Transplantation preparative regimens	
Cyclophosphamide (60 mg/kg) + busulfan (6 mg/kg)	1 (3)
Cyclophosphamide (60 mg/kg) + anti-T serotherapy	1 (3)
Cyclophosphamide (60 mg/kg) + fludarabine (175 mg/m^2) ± anti-T serotherapy	32 (89)
Cyclophosphamide (20 mg/kg) + total abdominal irradiation	2 (6)
Type of donor	
Matched sibling	26 (72)
Other matched related donor	10 (28)

19 pts evaluables au dernier FU (lesquels ?)

- 15 (79%) > ou = 1 anomalie
- Sd obstructif : 10 (53%),
- Bronchiolite : 3 (16%),
- Sd restrictif : 4 (21%)
- Augmentation VR : 60%
- DLCO N

Pas de cGvHD associée

Interstitial lung disease in an adult with Fanconi anemia: clues to the pathogenesis
Rubinstein et al, Am J Med Genet. 1997 Mar 31;69(3):315-9

Homme de 38 ans, PID traitée par corticoïdes et bactrim

- Dyspnée depuis l'age de 20 ans
- 25 ans : anomalies interstitielles debutante RP
- Thrombocytopenie puis pancytopenie progressed to pancytopenia.
- Anomalies osseuses, cardiaque, renale, cutanée, hepatique et neurologique evocatrices de FA
- Caryotype 46,XY, exces marqué de cassures chromosomique au DEB
- Tabagisme actif jusqu'à 32 ans
- 38 ans, scanner : fibrose des 2 lobes superieurs, aspect en rayon de miel des bases et bronchiectasies. EFR : sd restrictif modéré et sd restrictif?
- α1AT N

    - **A l'époque pas d'autre cas rapporté de PID associé au FA (registre IFAR)**
    - **Pas d'autre cas publié depuis**

Manifestations Hépatiques

Incidence of liver abnormalities in Fanconi anemia patients

Am J Hematol, 2012

Caroline Masserot-Lureau,[1] Nadir Adoui,[2] Françoise Degos,[3] Cédric de Bazelaire,[4] Jean Soulier,[5,6] Sylvie Chevret,[7] Gérard Socié,[6,8] and Thierry Leblanc[1*]

64 patients FA, âge médian 14 ans (5.5 mois ; 55.7 ans)

FANCA (n= 53), FANCC (n = 1); FANCG(n = 4), FANCD2 (n = 5), and 1 downstream.

FU médian 4 ans (range 2 mois à 32.5 ans)

44 sans androgènes : 7 anomalies biologique hépatiques persistantes (dont 2 FR)

- 2 pts très jeune, cytolyse sévère persistantes après 7 & 16 ans de FU
- 3 pts anomalies modérées

20 androgenes : 17/20 anomalies biologiques persistantes, y compris à distance de l'arret

- Adenomes, hyperplasies canaux biliaires, surcharge martiale

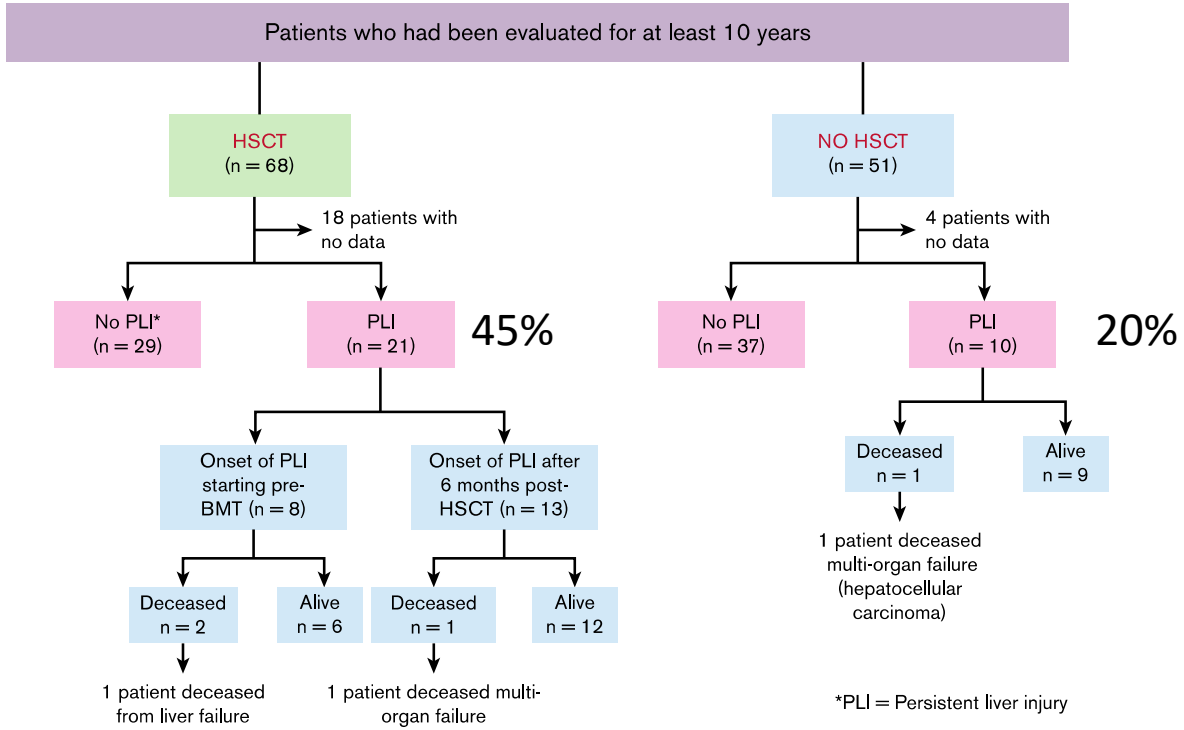
Manifestations Hépatiques

Liver abnormalities are frequent and persistent in patients with Fanconi anemia

2024, Snyder et al

blood advances

Persistent Liver Injury (PLI) : ALAT & ASAT > N, 3 fois (>1 mois)



Cohorte greffée :

- Age médian HSCT 6,7 ans
- Age médian 1eres anomalies 7,1 ans (6,1-9,3)
- Médian max ASAT 6 N, ALAT 7 N
- Age médian max 13,4 ans

Cohorte non greffée :

- Age médian 1eres anomalies 12,3 ans (2,8-15,7)
- Médian max ASAT 4 N, ALAT 8 N
- Age médian max 23 ans

Manifestations Hépatiques

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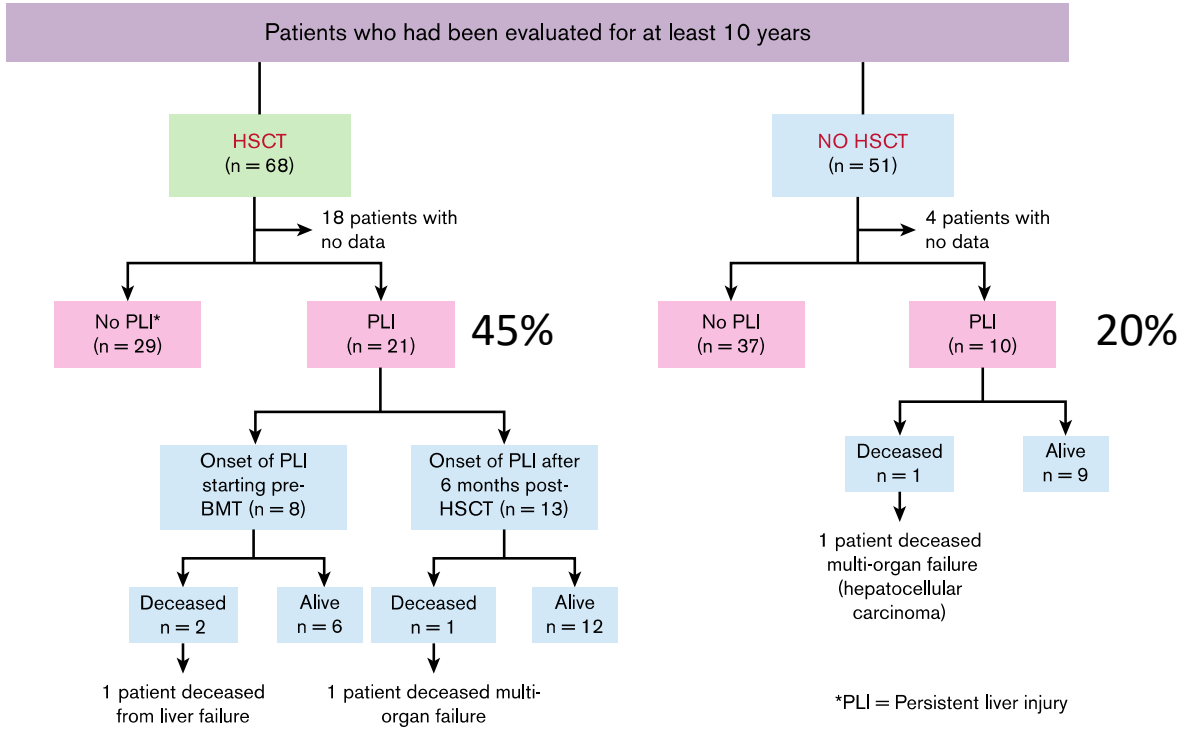
blood advances

Persistent Liver Injury (PLI) : ALAT & ASAT > N, 3 fois (>1 mois)



	HSCT cohort (n = 21)	Non-HSCT cohort (n = 10)
Imaging findings, n (%)	n = 20 with imaging	n = 8 with imaging
Normal liver	11 (55)	5 (62.5)
Biliary duct dilatation	2 (10)	1 (12.5)
Coarse/cirrhotic liver	0	1 (12.5)
Steatosis	1 (5)	1* (6.3)
Periportal edema	3 (15)	0
Hepatomegaly	0	0
Splenomegaly	0	0
Nodules/discrete lesions	1 (5)	0
Increased stiffness	2 (10)	1* (6.2)
Hepatosplenomegaly, n (%)	2 (9.5)	0
Evidence of portal hypertension, n (%)	n=2	n=1
Ascites	1	1
Splenomegaly	2	0
Thrombocytopenia	1	0
Varices	0	0
Jaundice, n (%)	4 (19)	1 (10)
Pruritus, n (%)	2 (9.5)	0
Encephalopathy, n (%)	0	0
History of gastrointestinal bleeding, n (%)	1 (4.8)	1 (10)

Manifestations Hépatiques

Liver abnormalities are frequent and persistent in patients with Fanconi anemia

2024, Snyder et al

blood advances

Table 5. Multivariate analysis of PLI in individuals with FA who received HSCT

Variable	OR	*P* value
Age (y) at HSCT, median (IQR)	0.84 (0.7-0.97)	**.04**
Complementation group		
Non-*FANCA*	2.88 (0.78-11.76)	.12
FANCA	1	
Conditioning regimen with TBI		
Yes	15.5 (2.44-304.54)	**.01**
No	1	
TA-TMA		
Yes	0.27 (0.07-0.91)	**.045**
No	1	

Table 6. Univariate analysis of clinically significant liver injury in individuals with FA who did not receive HSCT

Variable	PLI* (n = 10)	No PLI (n = 37)	*P* value
Sex, n (%)			.67
Female	6 (60)	17 (45.9)	
Male	4 (40)	20 (54.1)	
Race, n (%)			
Caucasian	10 (100)	35 (94.6)	.75
African American	0	0	
Hispanic	0	1 (2.7)	
Asian	0	1 (2.7)	
Complementation group, n (%)			
FANCA	5 (55.6)	29 (80.6)	.26
Non-*FANCA*	4 (44.4)	7 (19.4)	
Androgen use, n (%)			
Yes	8 (80)	35 (94.6)	.41
No	2 (20)	2 (5.4)	

Manifestations Hépatiques

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2 patients décédés d'hépatopathie chronique

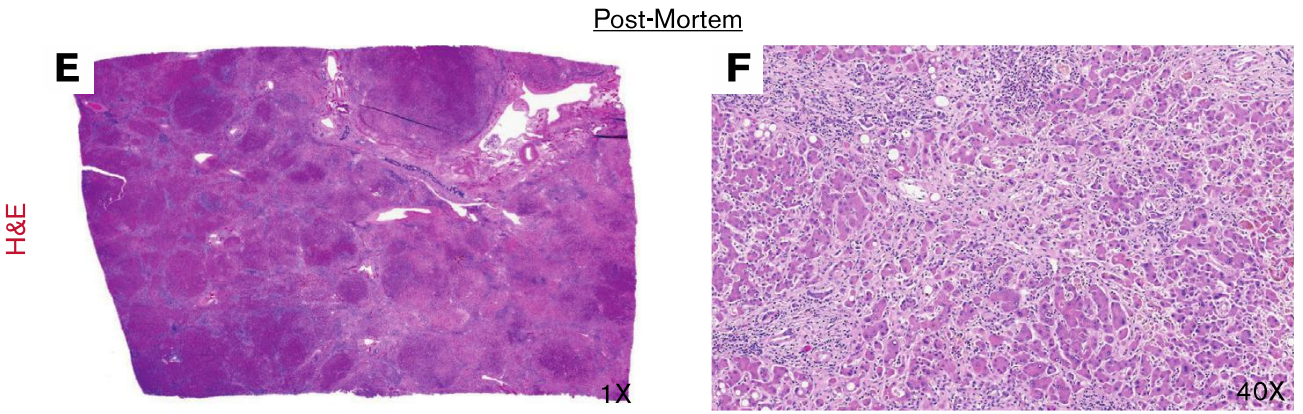
1 sans info

2nd : allogreffe avec TBI 4,5 Gy

- **Cytolyse hépatique 5 ans post HSCT, histo cGvHD**
- **Hepatopathie cholestatique 17 ans post allogreffe**

Evolution défavorable malgré ttt

Décès



Manifestations Hépatiques

Conclusions :

- Anomalies hépatiques fréquentes
- Le plus souvent bénignes
- Surveillance échographique (IRM) /an si anomalies ou androgènes
- Surveillance échographique / 2 ans après 20 ans sinon (CHC)
- Biopsie si anomalies sévères uniquement
- Exploration surcharge martiale

CRMR Aplasies médullaires acquises et constitutionnelles

Hôpital Saint-Louis

Hôpital Robert Debré

IUH St Louis

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SFGM TC
Société Francophone de GREFFE DE MOELLE et de Thérapie Cellulaire

2016 EBMT
European Society for Blood and Marrow Transplantation

French reference center for AA : information

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