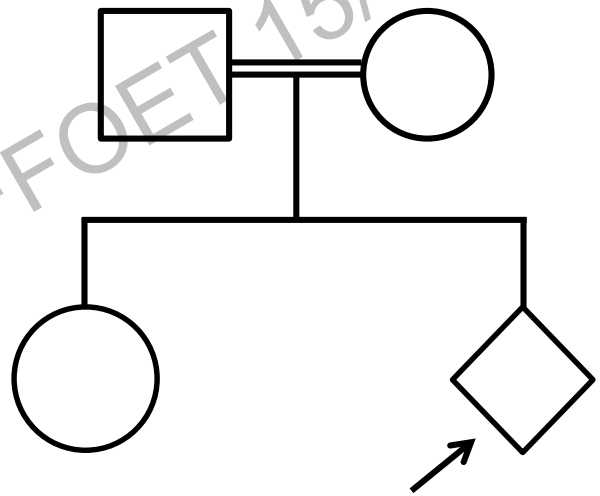
SoFFœt
Société Française de Fœtopathologie

A rare case of neonatal death

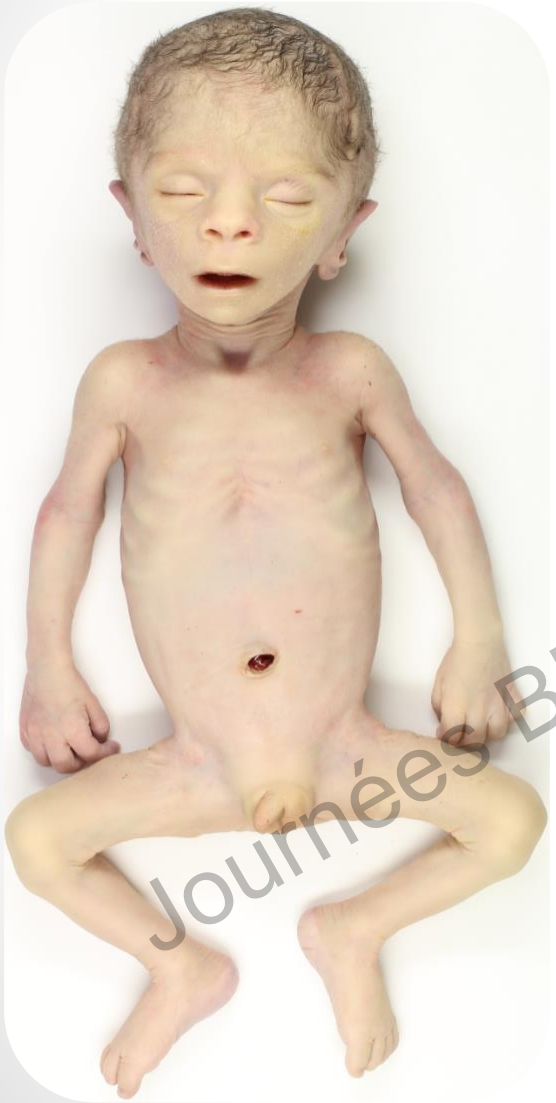
Adeline BONNARD
DÉPARTEMENT DE GÉNÉTIQUE - FŒTOPATHOLOGIE
Hôpital ROBERT DEBRÉ, PARIS

Prenatal history

- 26 y/o G2P1 women:
  - Blood related husband
  - Uneventful first pregnancy
- During 2nd pregnancy:
  - 1st trimester: normal morphology
  - 2nd trimester:
    - IUGR (normal dopplers)
    - Intestinal hyperechogenicity
    - Unwanted investigations
  - 3rd trimester: ascites and oligohydramnios
    - 36 + 3 GW : emergency cesarean section for fetal bradycardia

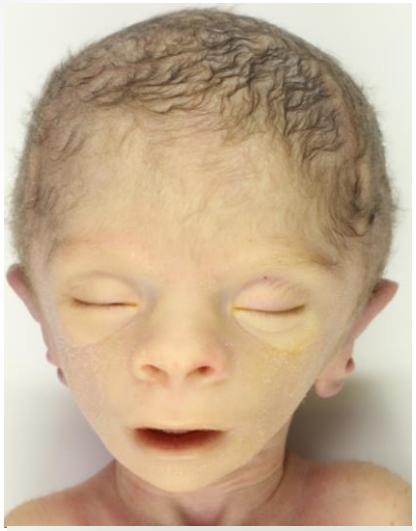


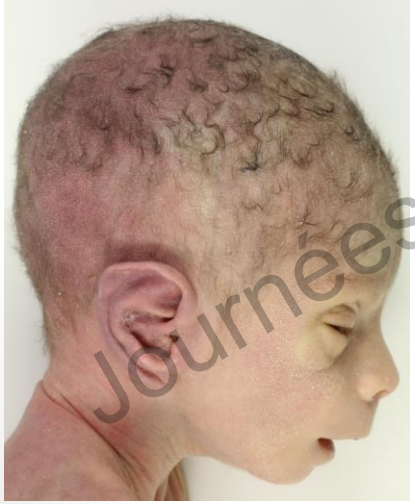
Case report



- Birth presentation:
  - Bradycardia/respiratory distress (intubation M2)
  - Deceased at H5 in intensive care
  - Biology:
    - Severe lactic acidosis
    - Massive disseminated intravascular coagulation
- Morphology:
  - Hypotrophic - severe growth retardation (~31 GW)
  - Thin adipose tissue
  - Pale skin
  - No obvious malformation

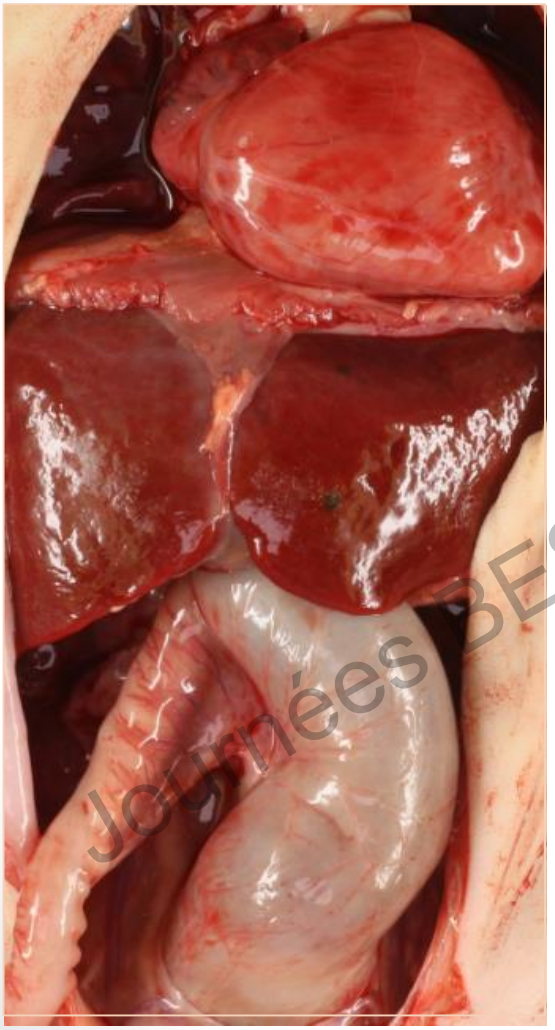
Case report





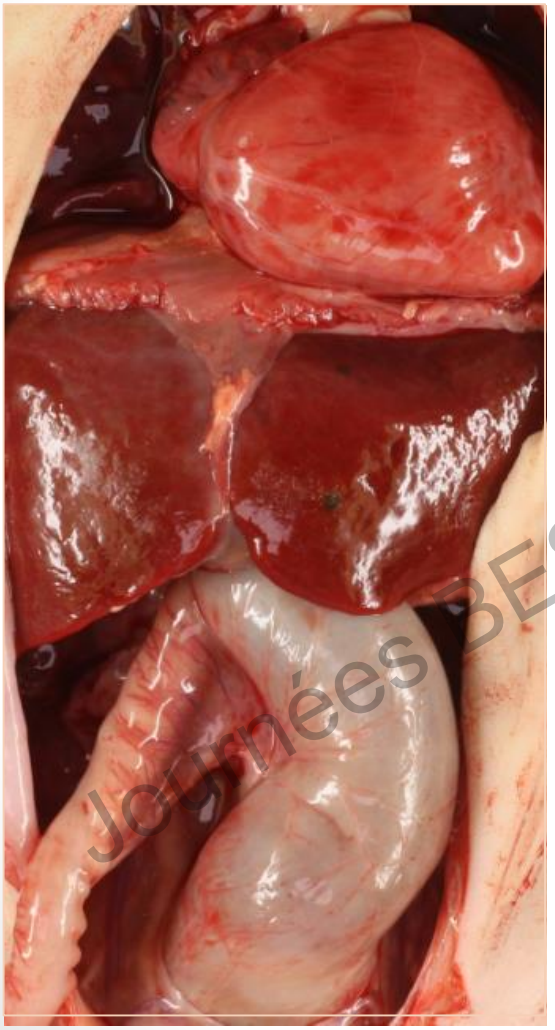
- Birth presentation:
  - Bradycardia/respiratory distress (intubation M2)
  - Deceased at H5 in intensive care
  - Biology:
    - Severe lactic acidosis
    - Massive disseminated intravascular coagulation
- Morphology:
  - Hypotrophic - severe growth retardation (~31 GW)
  - Thin adipose tissue
  - Pale skin
  - No obvious malformation

Visceral examination

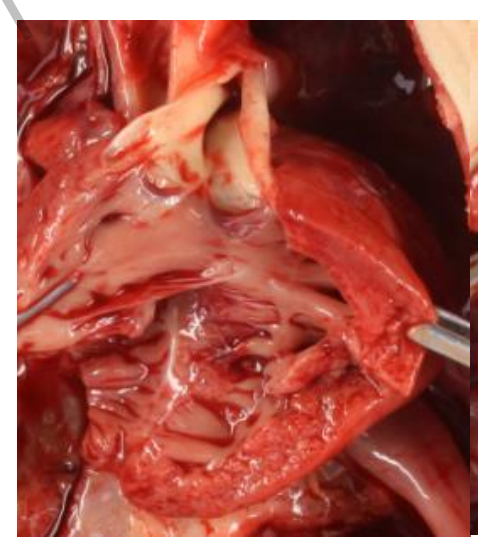


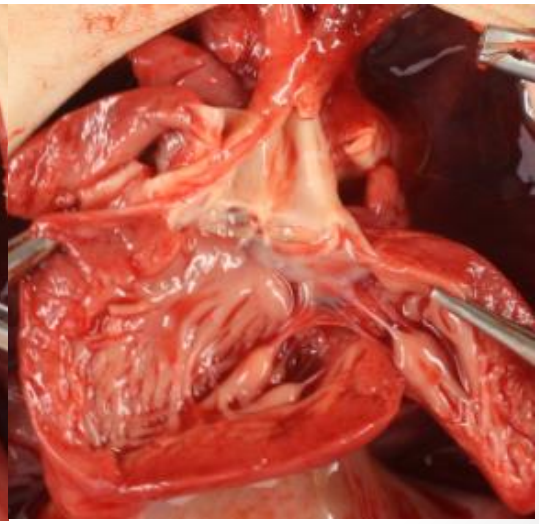
- Absence of visceral malformation
- Hypoplastic liver, kidneys and adrenals glands

Visceral examination

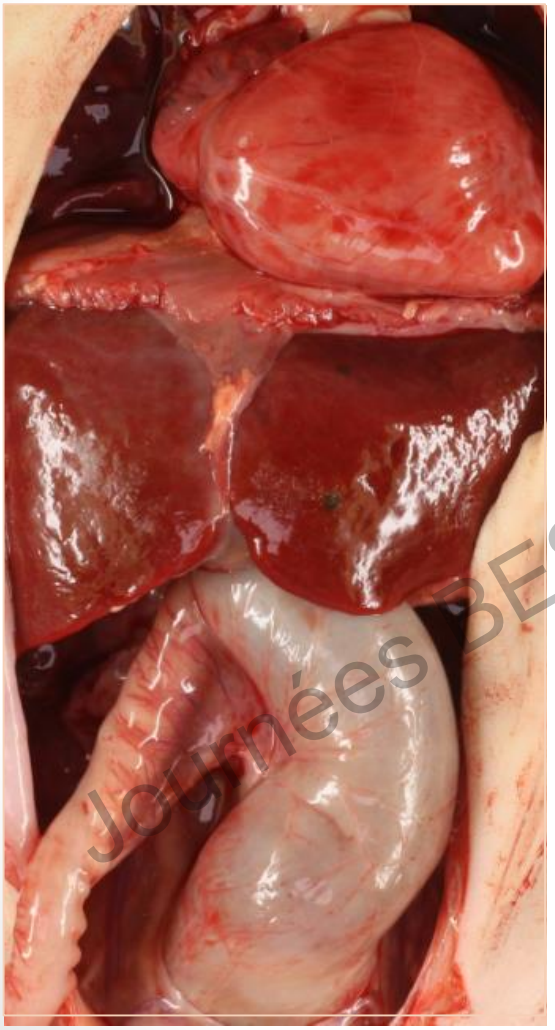


- Absence of visceral malformation
- Hypoplastic liver, kidneys and adrenals glands
- Cardiomegaly



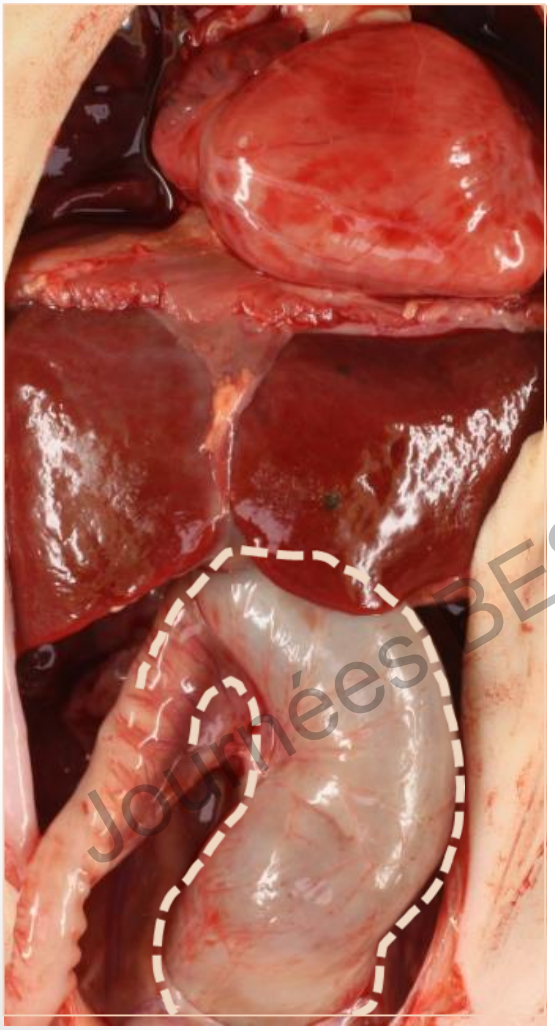


Visceral examination

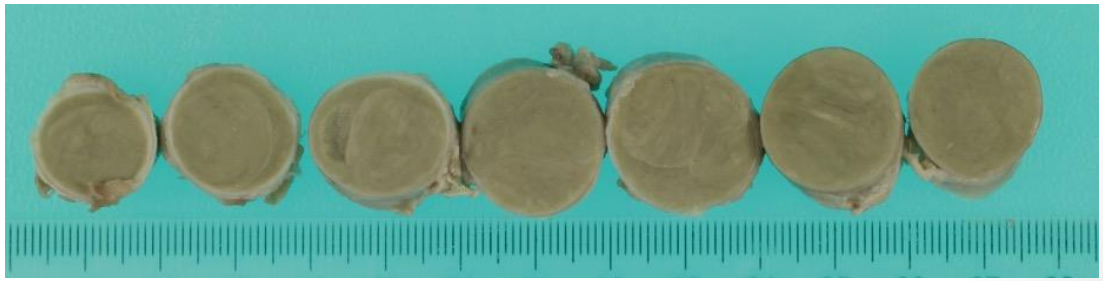


- Absence of visceral malformation
- Hypoplastic liver, kidneys and adrenals glands
- Cardiomegaly
- Rusty liver

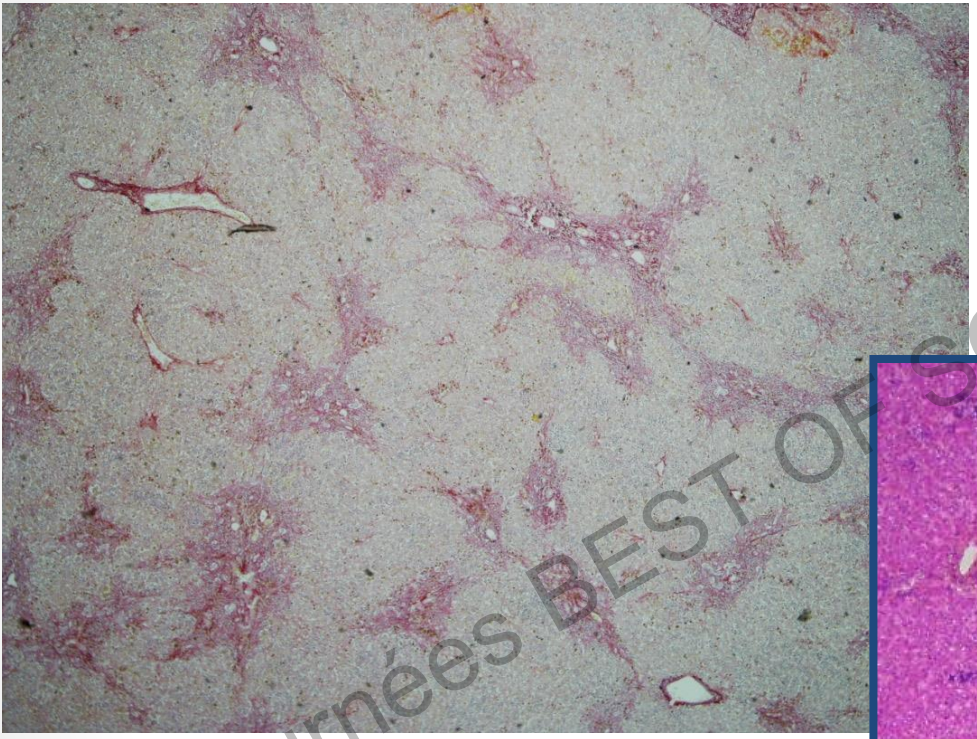
Visceral examination



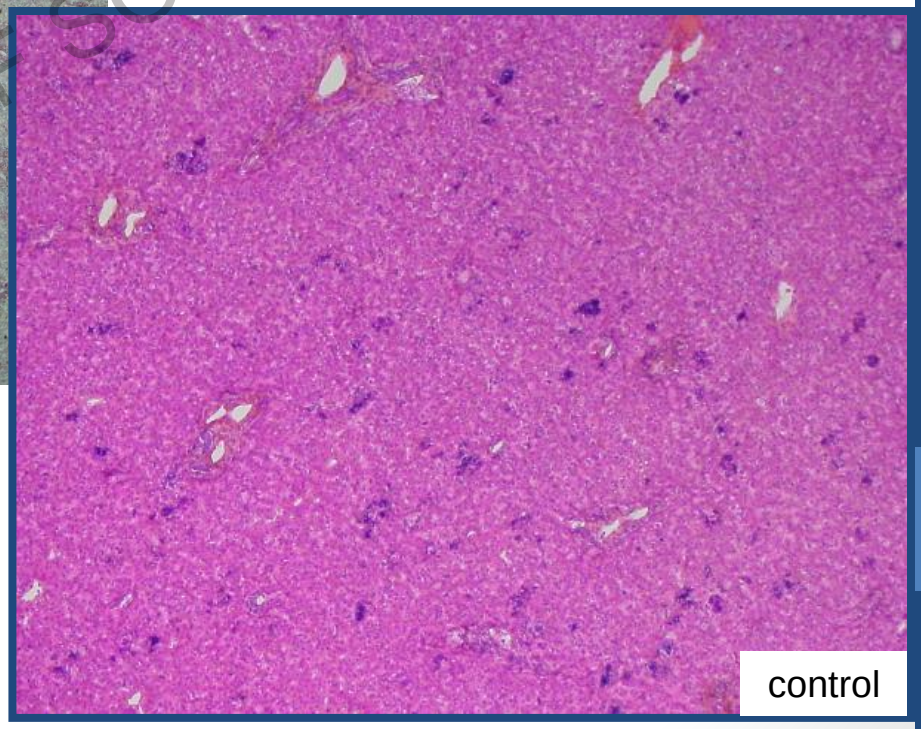
- Absence of visceral malformation
- Hypoplastic liver, kidneys and adrenals
- Cardiomegaly
- Rusty liver
- Dilatation of the sigmoid
  - Meconium plug - elastic meconium
  - No rectal stenosis



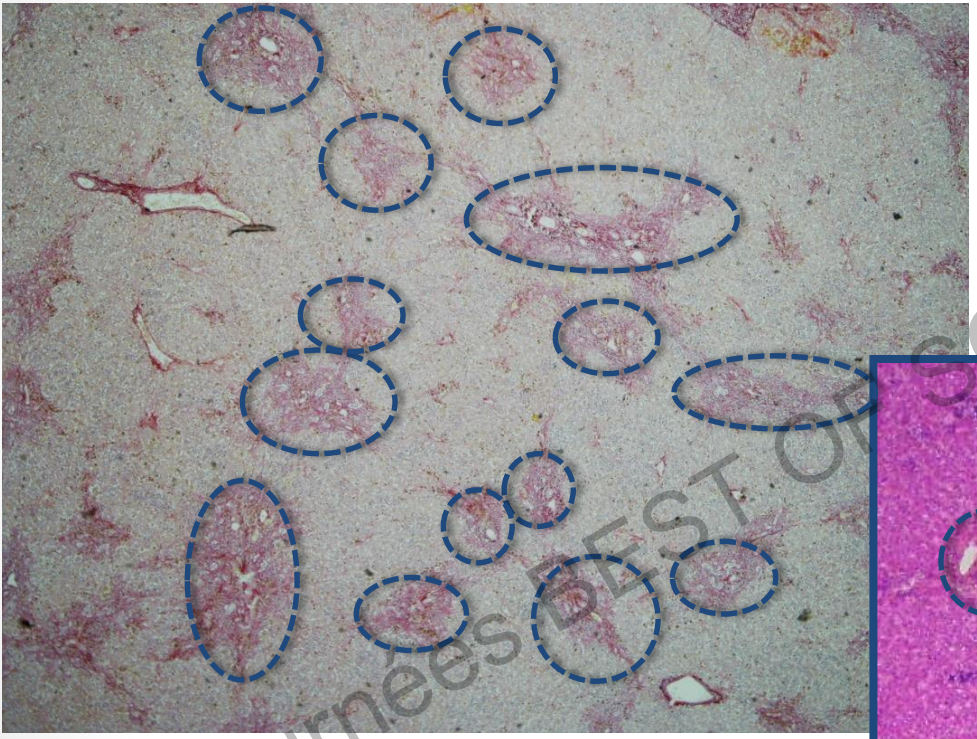
Histologic examination:
Liver fibrosis

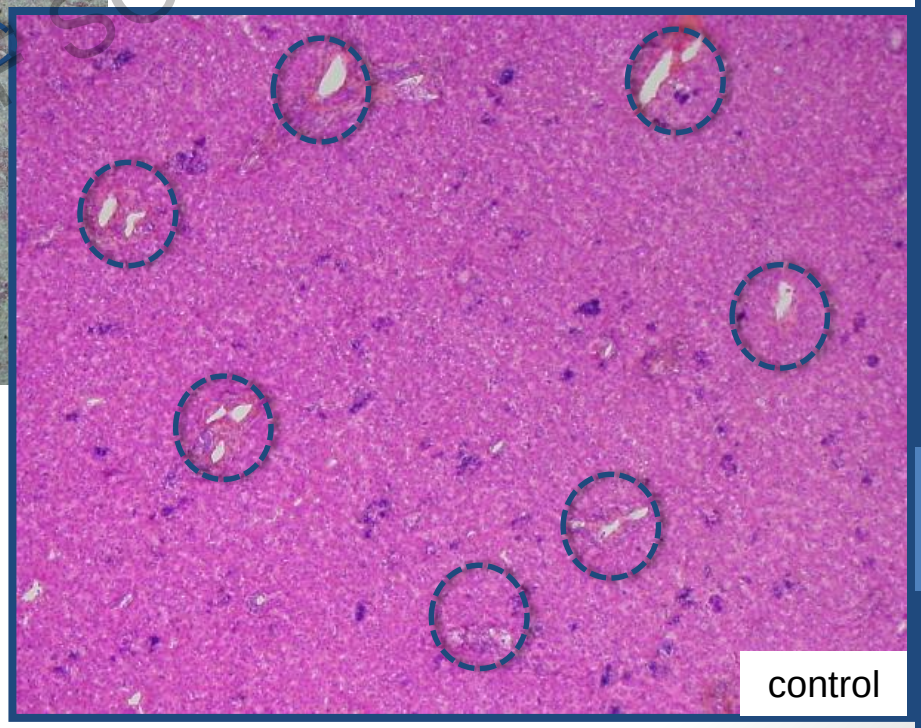


- Enlarged and fibrous periportal spaces with septa
- Hazardly arrangement of the portal tracts



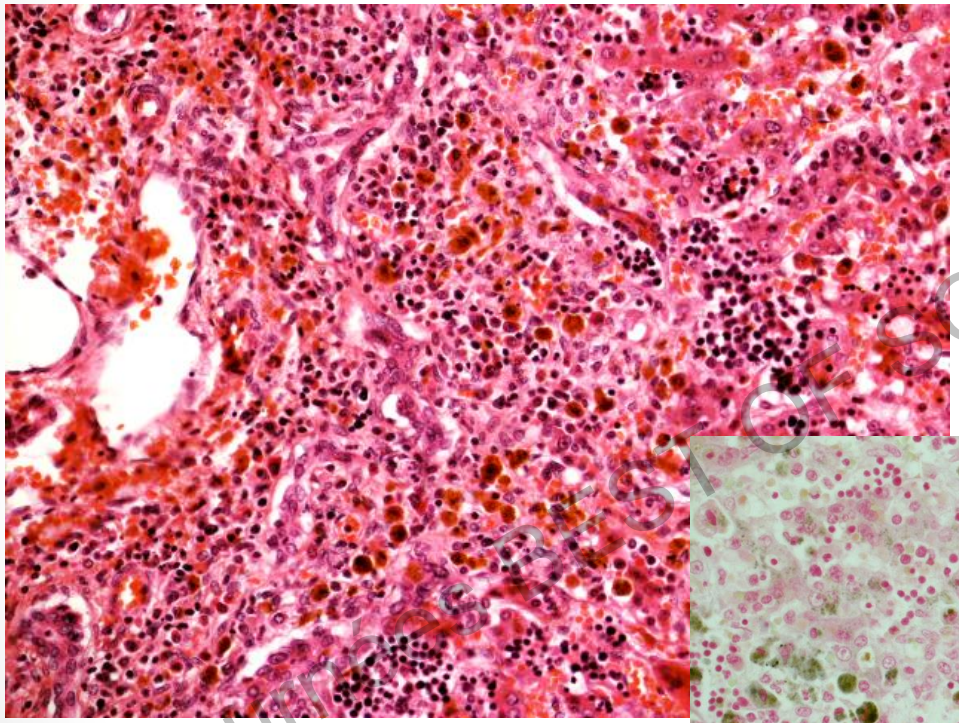
Histologic examination:
Liver fibrosis



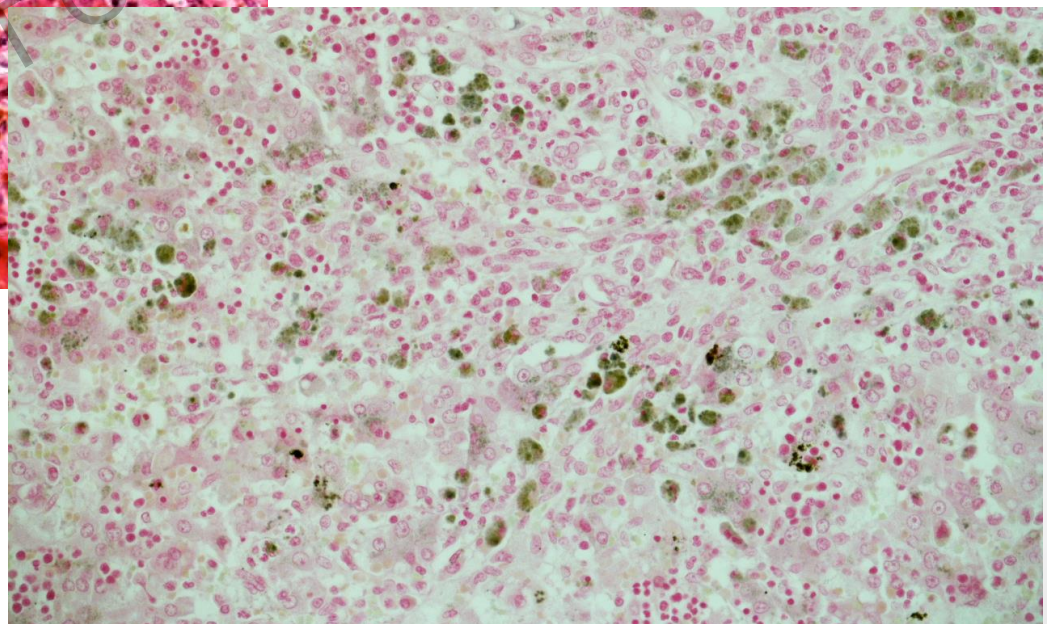


- Enlarged and fibrous periportal spaces with septa
- Hazardly arrangement of the portal tracts

Histologic examination:
Iron overload

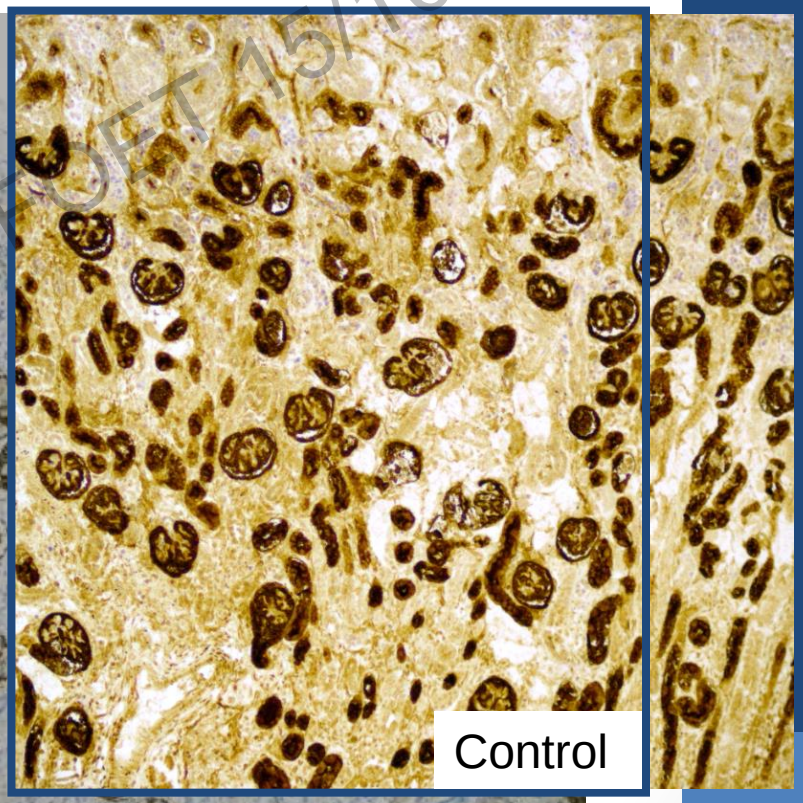


- Perls staining:
  - Hepatocytic
  - Macrophagic ++
  - Extrahepatic



- C5b9 immunostaining:
  - Negative in hepatocytes

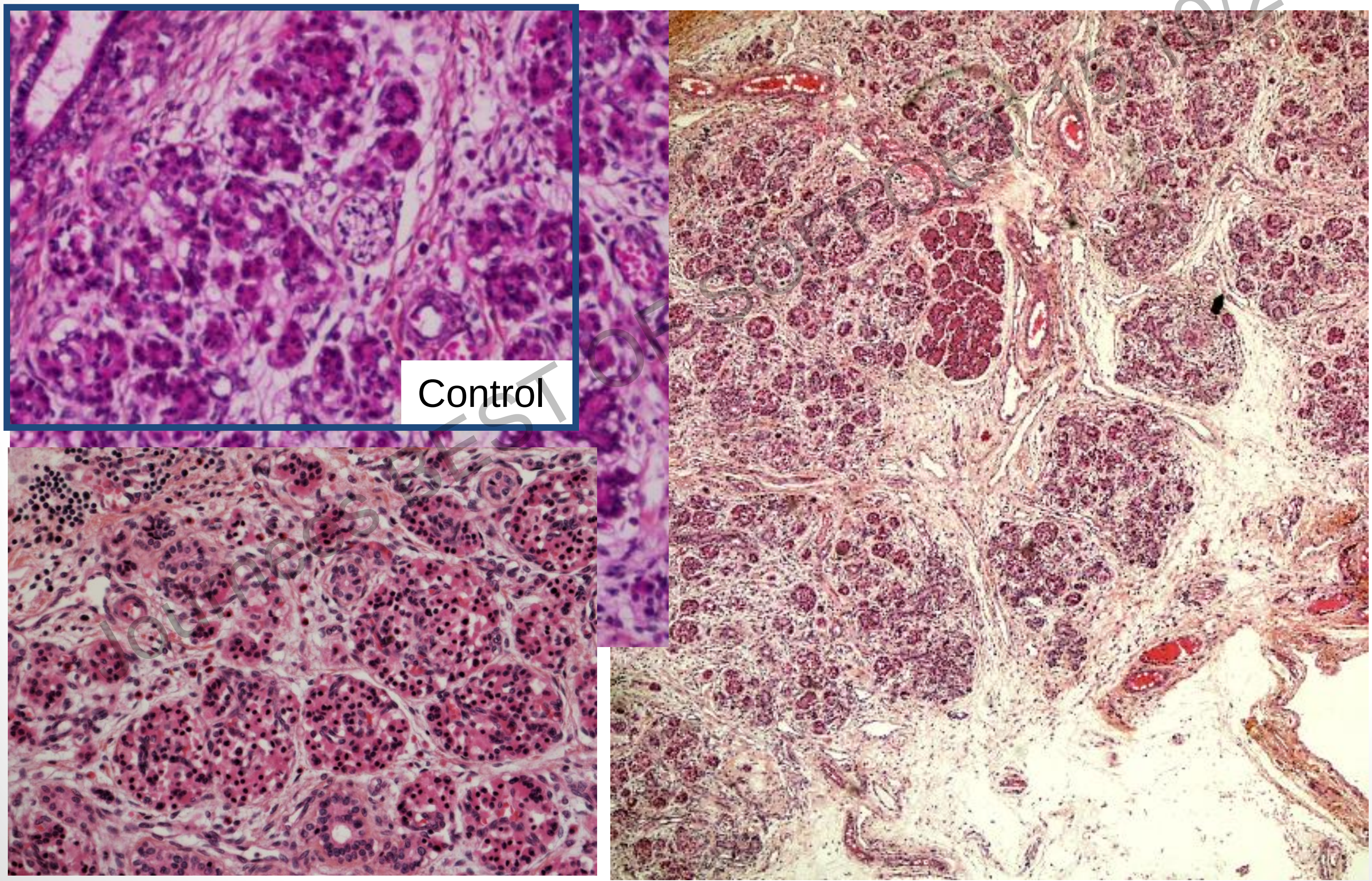
Histologic examination:
Renal tubular dysgenesis



- CD10 immunostaining: rarefaction of proximal tubules

Histologic examination:

Pancreatic fibrosis



To summarize

- Lactic acidosis
- IUGR, oligohydramnios

Neonatal death

- Iron overload : SRE, intra and extrahepatic
- Renal tubular dysgenesis

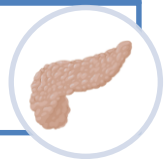
Neonatal hemochromatosis

- Placental examination
- Complete phenotypage
- Immunomarking
- Array CGH Analysis
- Maternal history

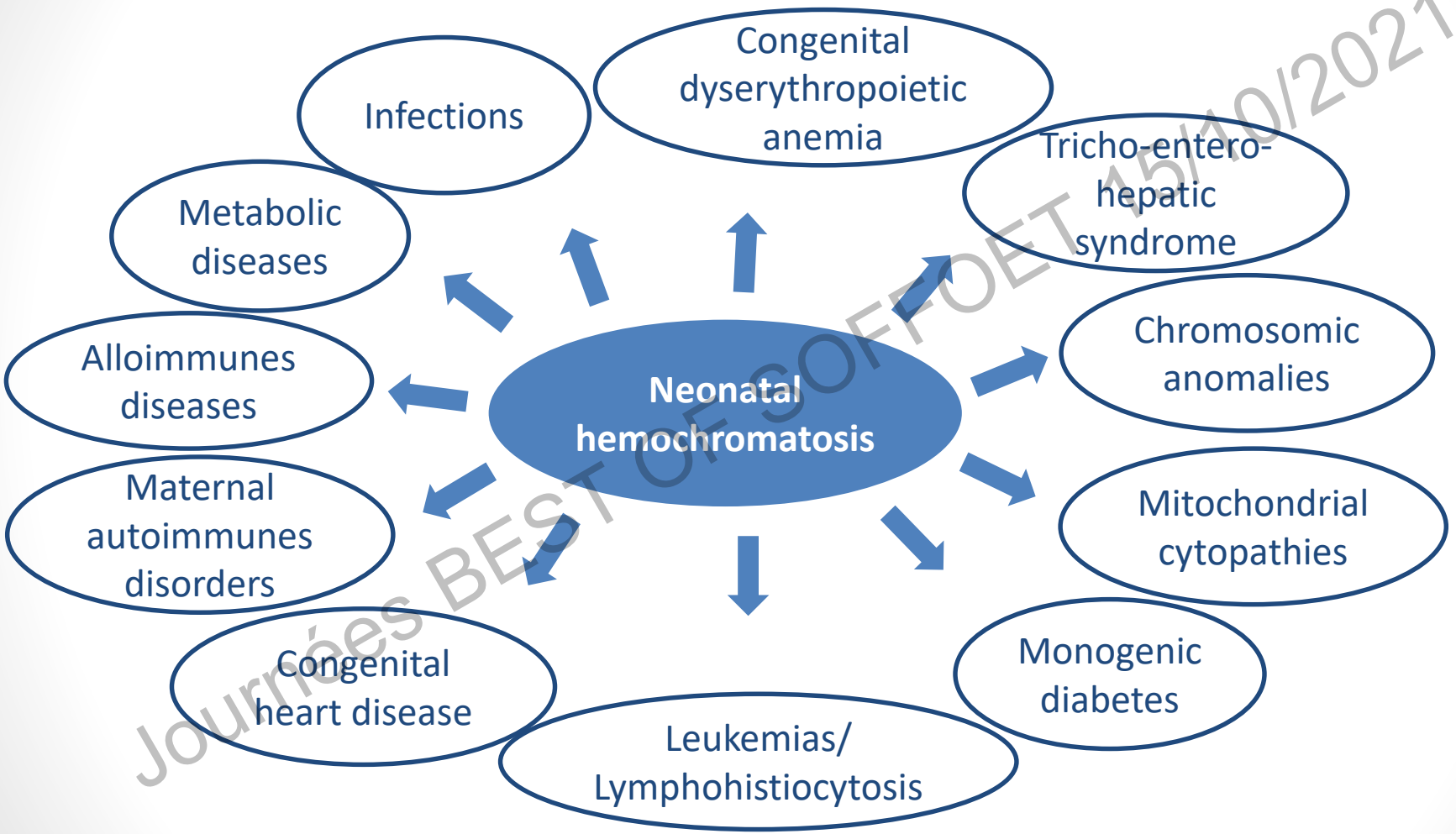
Negative features

- Pancreatic fibrosis
- Meconial plug

Pancreatic exocrine insufficiency

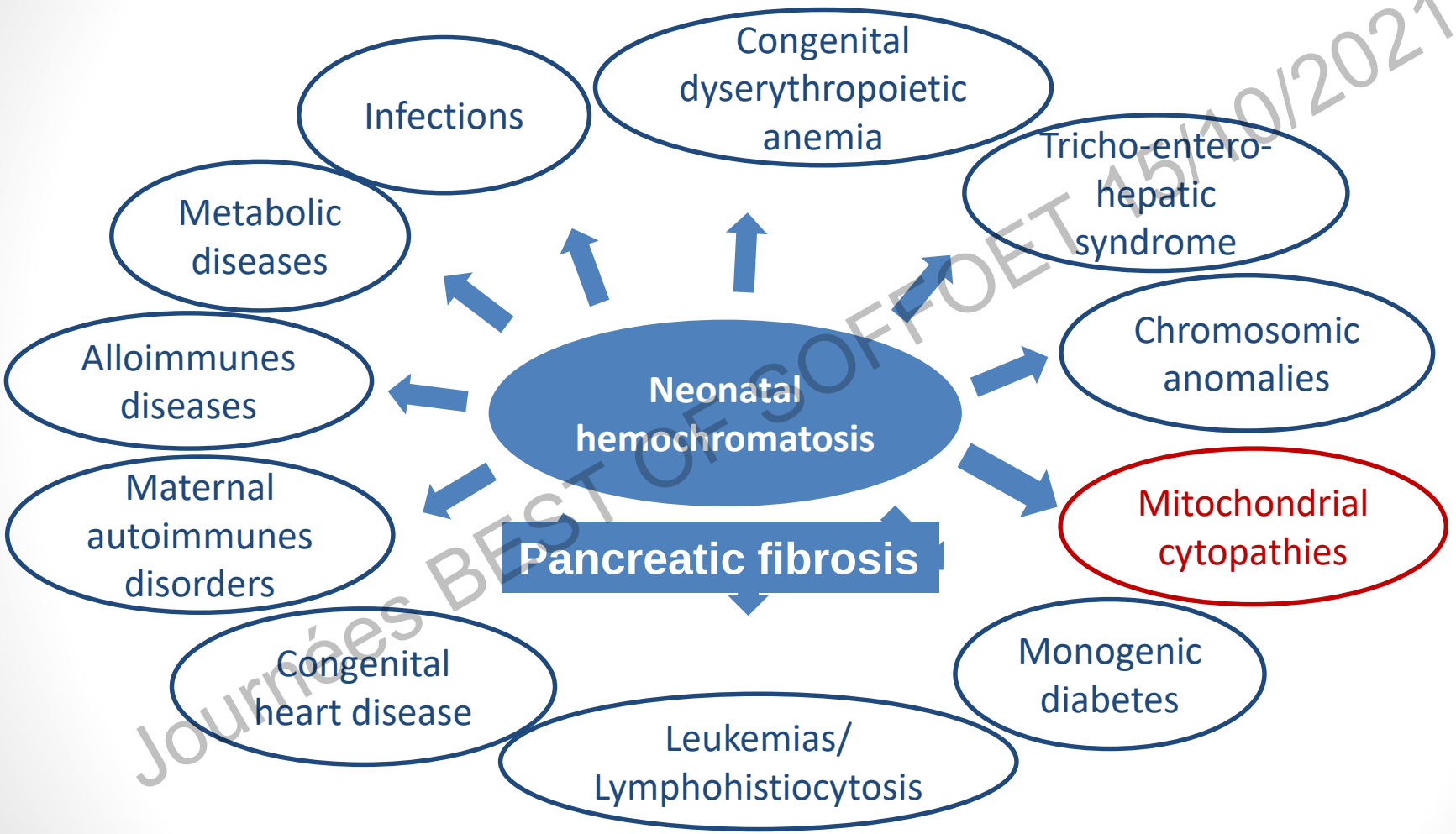


Hemochromatosis: a phenotype



Sergi et al. 2001

Hemochromatosis: a phenotype



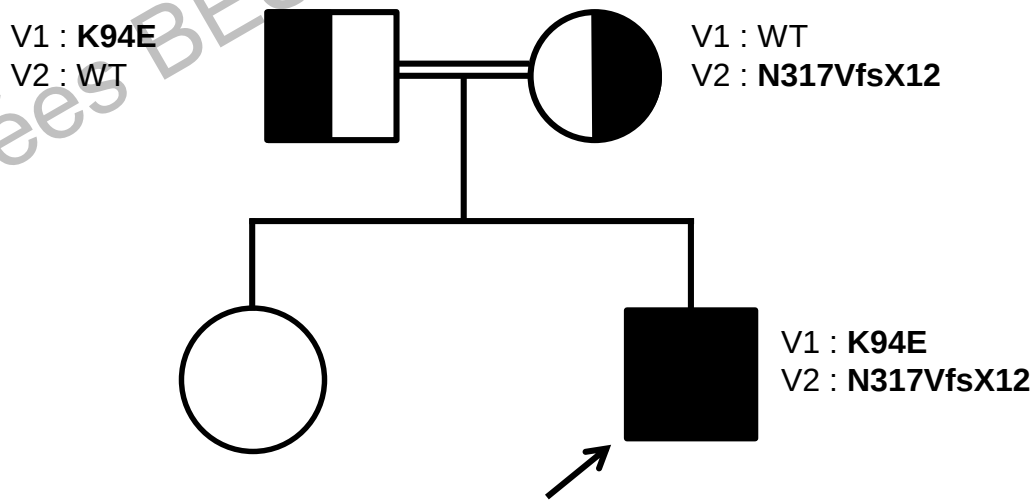
Sergi et al. 2001

Mitochondrial deficiency hypothesis

- Analysis of the respiratory chain on fibroblasts:
  - Moderate decrease of complex III (C III)

Mitochondrial deficiency hypothesis

- Analysis of the respiratory chain on fibroblasts:
  - Moderate decrease of complex III
- NGS of nuclear mitochondrial disease-related genes:
  - *BCS1L* (NM_004328) compound heterozygous mutations:
    - c.280A>G, p.Lys94Glu (probably pathogenic)
    - c.950_953del; p.Asp317ValfsTer12 (probably pathogenic)



BCS1L diseases

- Assembly of the respiratory chain (Complex III) *(Nobrega et al., 1992)*
  - Member of the AAA+ family (ATPases associated with diverse cellular activities)
  - Genotype-phenotype relationships is poorly understood

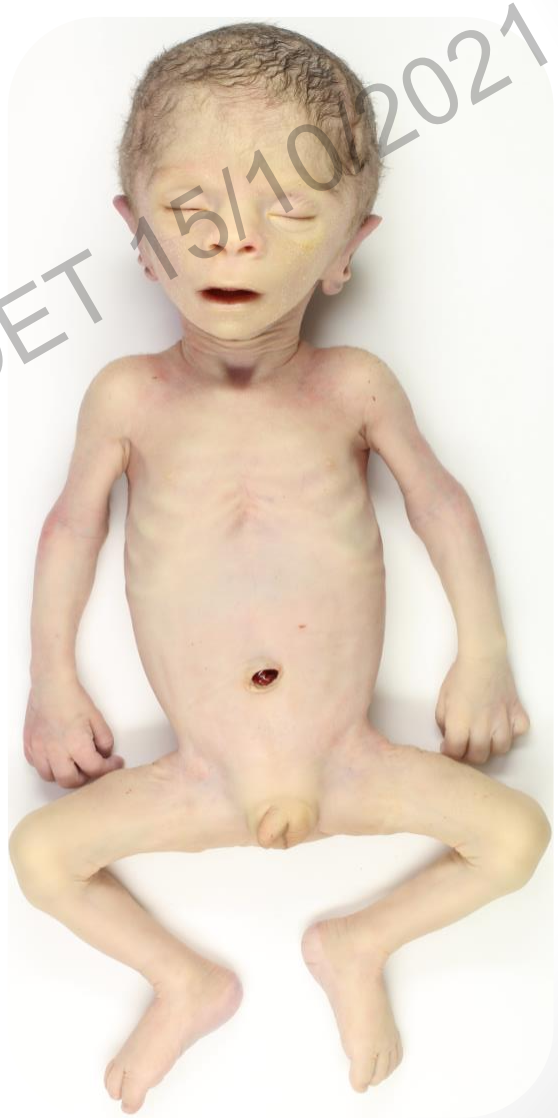
- BCS1L mutations lead to three main clinical phenotypes *(Ramos-Arroyo et al., 2009)*
  - GRACILE syndrome
  - Mitochondrial CIII deficiency
  - Björnstad syndrome

GRACILE Syndrome

(**G**rowth **R**etardation, **A**minoaciduria, **C**holestasis, **I**ron overload, **L**actic acidosis, **E**arly death)

- < 1/1 000 000
- Autosomal recessive
  - *BCS1L*
  - Rapidly fatal infantile disorder 1st observed in Finland
- Clinic:
  - IUGR, microcephaly
  - Hemosiderosis of the liver
  - Renal tubulopathy
  - Central Nervous System
    - Hypotonia/seizures
  - Worried looking facial expression and wrinkled skin due to the absence of subcutaneous fat *(Fellman et al. 1998)*

➢ **Pancreas exocrine atrophy**



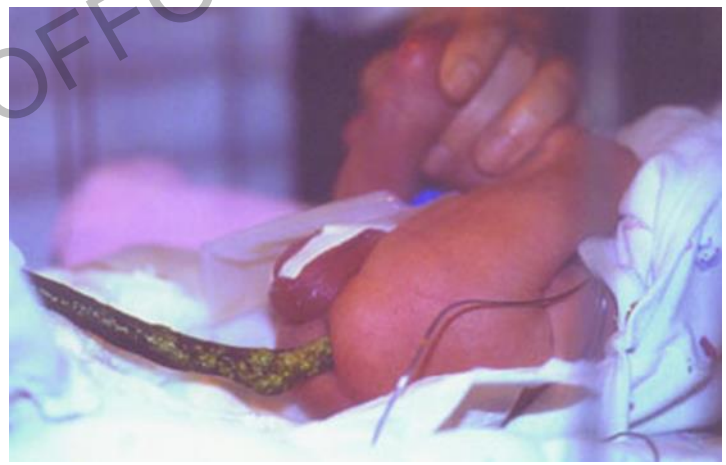
Pancreatic fibrosis in GRACILE syndrome

- Autopsy study of 17 newborn infant with GRACILE syndrome (Rapola et al. 2002):

TABLE 2. The Main Pathologic Features in the Organs of the Cases

	Liver					Pancreas	Kidney	
Case #	Fe-H	Fe-K	Steatosis	Fibrosis	Ductopenia	Exocrine Atrophy	Calcinosis	Tubular Dysgen
1	1 –	1 –	–	–	+	NA	2 +	–
2	3 +	2 +	–	–	+	+	–	+
3	3 +	3 +	–	–	+	+	–	+
4	3 +	3 +	+	–	–	–	–	+
5	4 +	2 +	–	–	?	NA	NA	NA
6	4 +	3 +	–	–	+	+	1 +	–
7	4 +	3 +	–	–	+	+	1 +	+
8	4 +	3 +	–	–	+	+	1 +	+
9	3 +	3 +	–	+	?	+	–	–
10	1 +	2 +	–	+	?	+	1 +	–
11	0	2 +	+	+	?	+	2 +	–
12	2 +	3 +	+	+	?	+	2 +	–
13	2 +	2 +	+	+	?	+	2 +	–
14	1 –	2 +	+	+	?	+	2 +	–
15	0	1 +	+	+	?	+	1 +	+
16	0	1 –	+	+	?	NA	2 +	–
17	0	1 +	+	+	?	+	2 +	–
18	1 –	2 +	+	+	?	NA	2 +	–

- Abnormal meconium in 2 cases report (De Meirleir et al. 2003):



Conclusion

- Case report of a rare cause of neonatal death with GRACILE syndrome
  - ~ 66 cases in 20 cases study
  - First report by Fellman et al. (1998)
- Association of 2 rare symptoms:
  - Hemochromatosis phenotype
  - Pancreatic fibrosis
- Mitochondrial disease with probable dysregulation of iron metabolism
  - Physiopathology not entirely understood

SoFFœt
Société Française de Fœtopathologie

Thank you for your attention