Hospices Civils de Lyon

SoFFœt
Société Française de Fœtopathologie

UNIVERSITÉ DE LYON

# SIGNES D'APPELS DES MALADIES MÉTABOLIQUES À L'AUTOPSIE VISCÉRALE

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# signes d'appel

## Examen externe

- **Ascite ou anasarque ++++**
- **RCIU**
- **Dysmorphie faciale**
- **Anomalies des OGE**
- **Anomalies cutanées**
- **Anomalies des membres et des extrêmités**
- **Anomalies PC et TN**

## Radiographies

- Épiphyses ponctuées
- Hypominéralisation +/-Fractures
- Synostose
- Asymétrie
- Dysostose multiple
- **Calcifications viscérales**

**Association de signes ++++**

# signes d'appel

## Examen interne

- **Viscéromégalie:** coeur, foie, rate
- **Cardiomyopathie hypertrophique**
- **Foie nodulaire ou de couleur anormale**
- **Reins kystiques**
- *Anomalies cérébrales : gyration, CC, FCP*

## Examen microscopique

- **Hémochromatose:** foie+/- autres organes
- **Stéatose**: foie, cœur, muscle, reins
- **Plaque ductale** (foie)
- **Reins kystiques+/- dysplasiques**
- **Cellules de surcharge**
- **Calcifications**
- *Anomalies cérébrales*

## Examen du placenta

- **Placentomégalie/ hydropique**
- **Cellules de surcharge**

# Quand penser à

**Maladies lysosomales (LSD)**

**Maladies peroxisomales**

**Déficit en arylsulfatase E: ARSE**

**Cholestérolopathies**

N-CDG
(O-CDG)

**Glycogénose IV (GSD IV)**

**Déficit de l'oxydation des acides gras**

**Cytopathies mitochondriales**

**Pyruvate Dehydrogenase deficiency (PDH)**
**Pyruvate Carboxylase deficiency**

**Déficit en transaldolase**

**Aminoacidopathies et aciduries organiques**

- **Neu-Laxova syndrome**

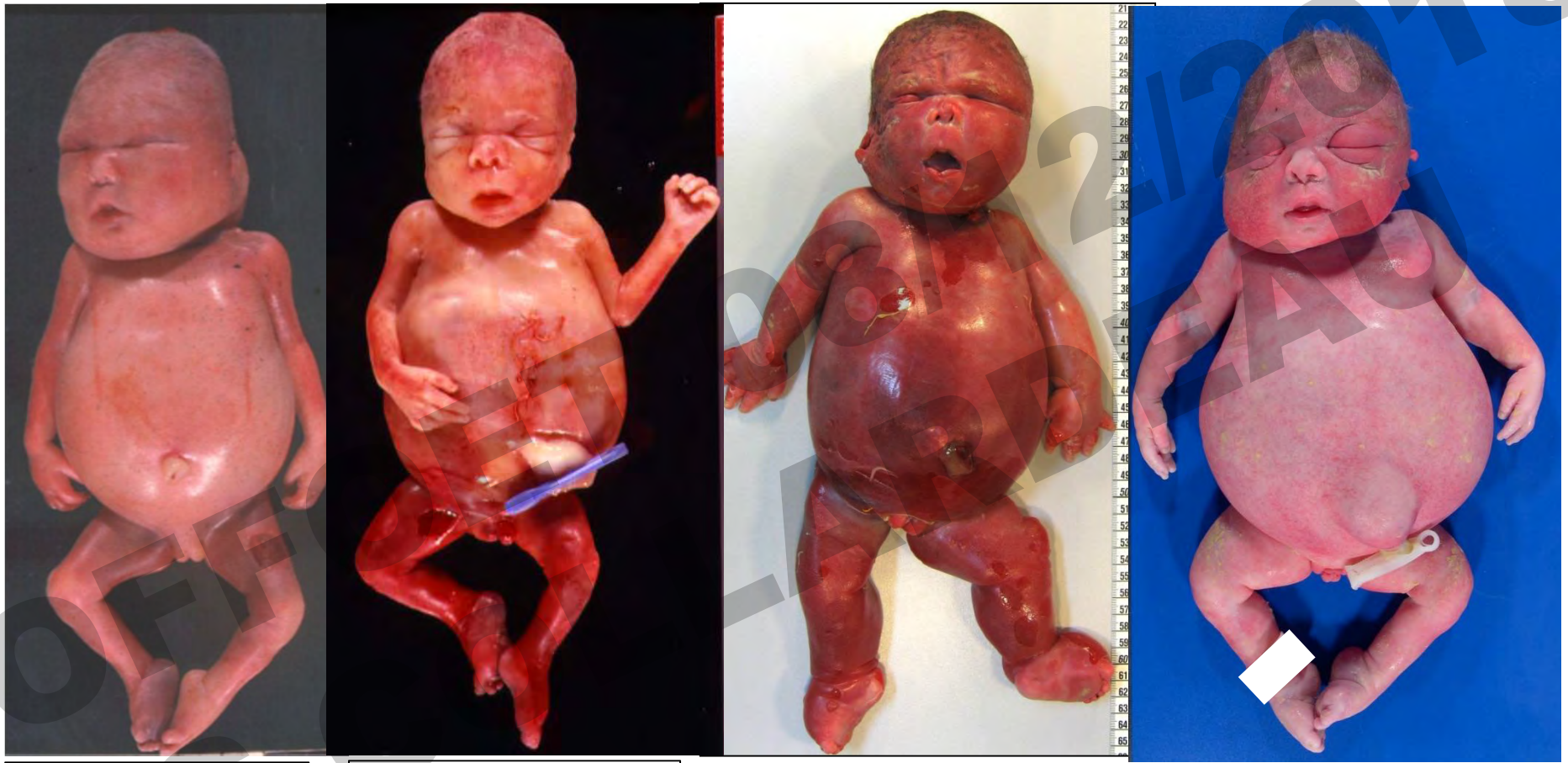
Anomalies du métabolisme du **phosphate, calcium et vitamine**

- **hypophosphatasia**
- **generalized arterial calcification of infancy (GACI)**

**Porphyries héréditaires**

- **Congenital erythropoietic porphyria**

# Maladies lysosomales



MPS IVA, 25 GW

ISSD, 26 GW
*Courtesy of P Dechelotte*

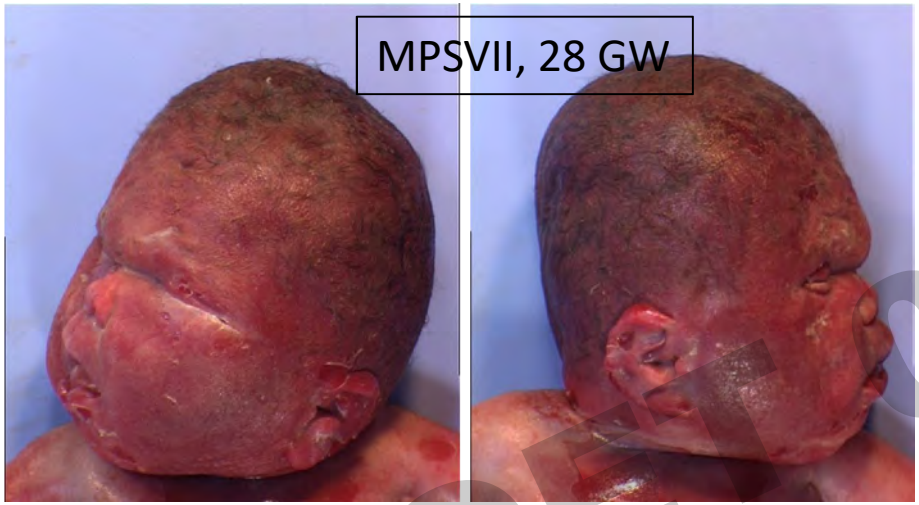
MPS VII,28 GW

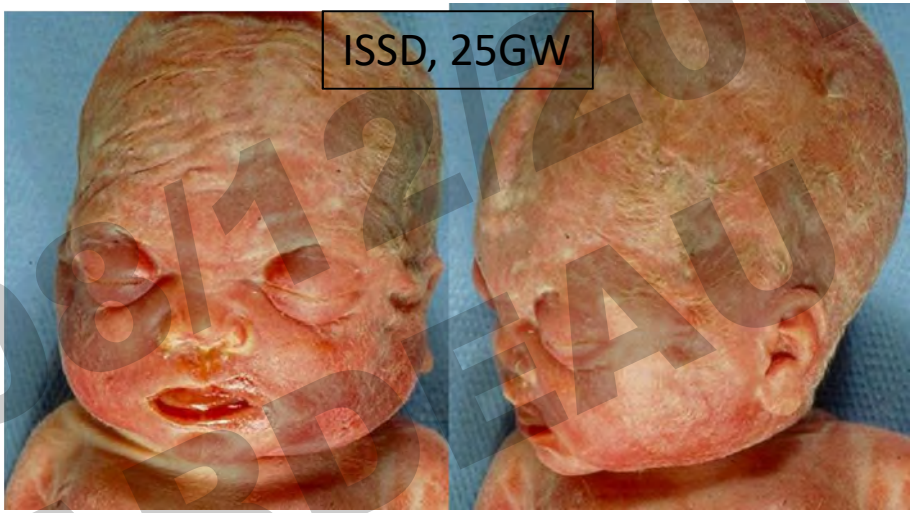
Galactosialidosis, 29GW
*Courtesy of D Carles*

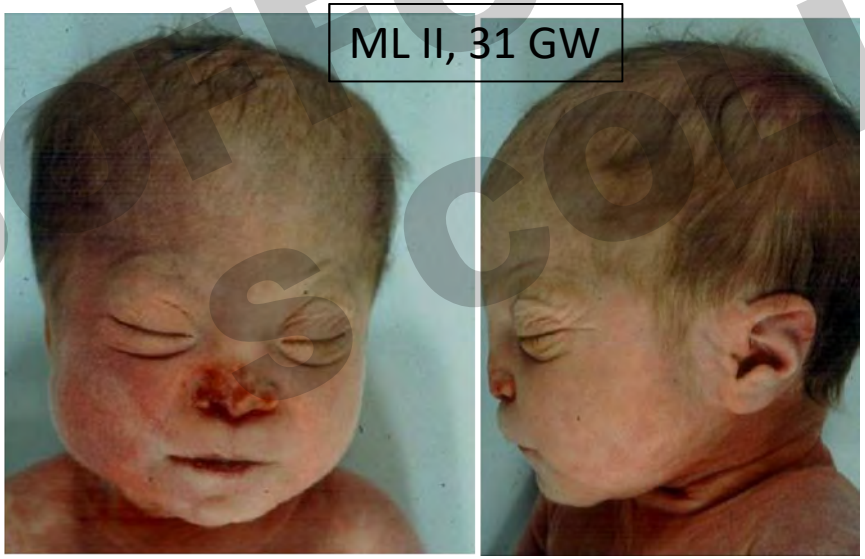
**Hydrops with prominent ascites (hepatomegaly) and abdominal distention**

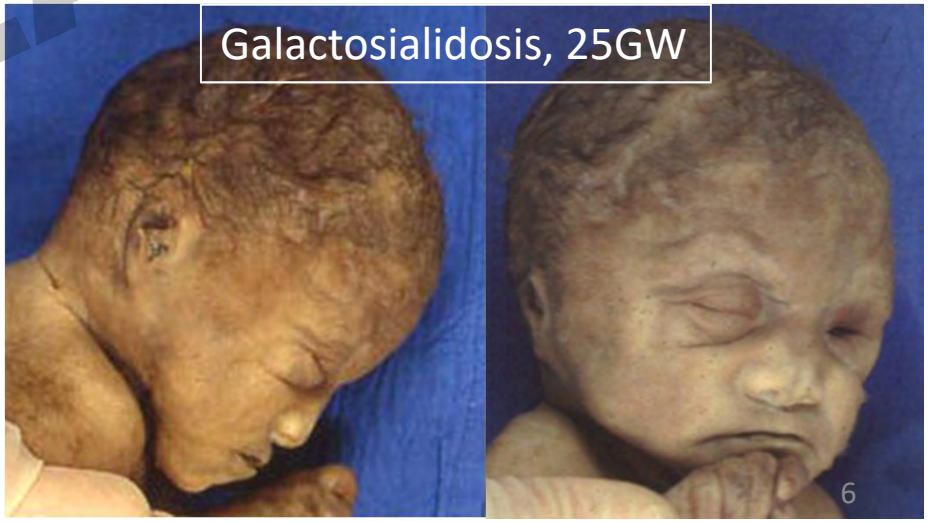
# Maladies lysosomales

## Hypoplasie de l'étage moyen: faciès de Binder

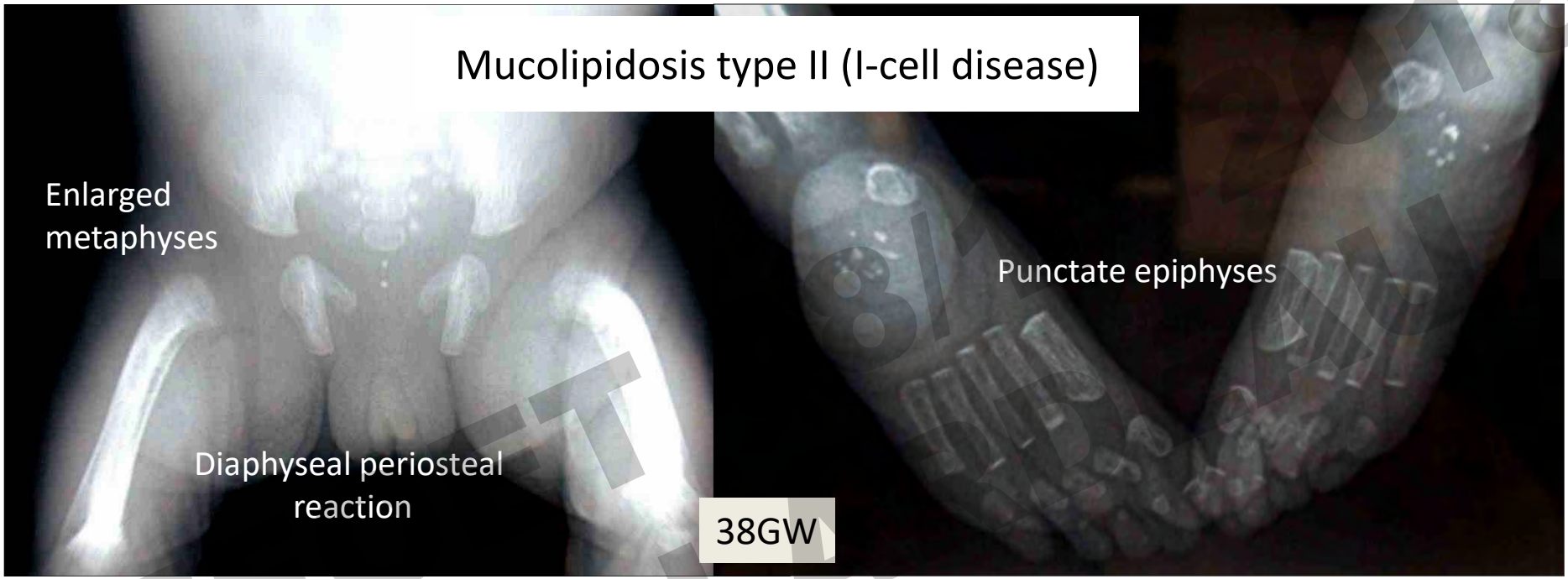


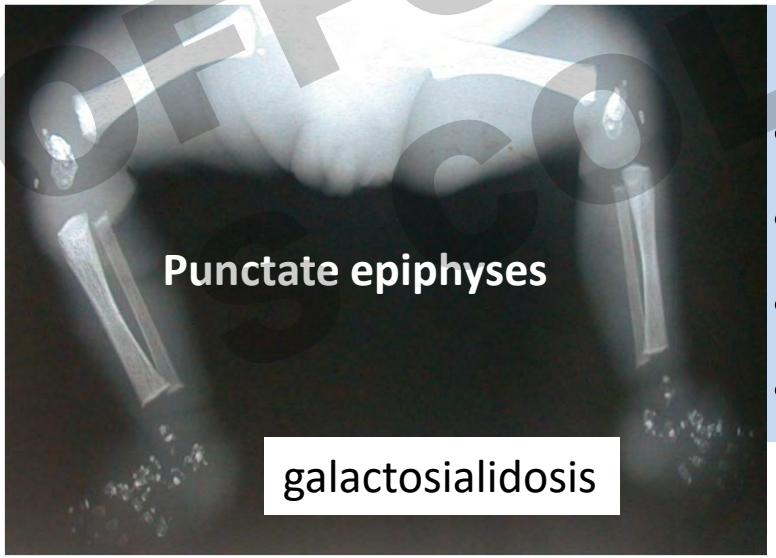



# Maladies lysosomales



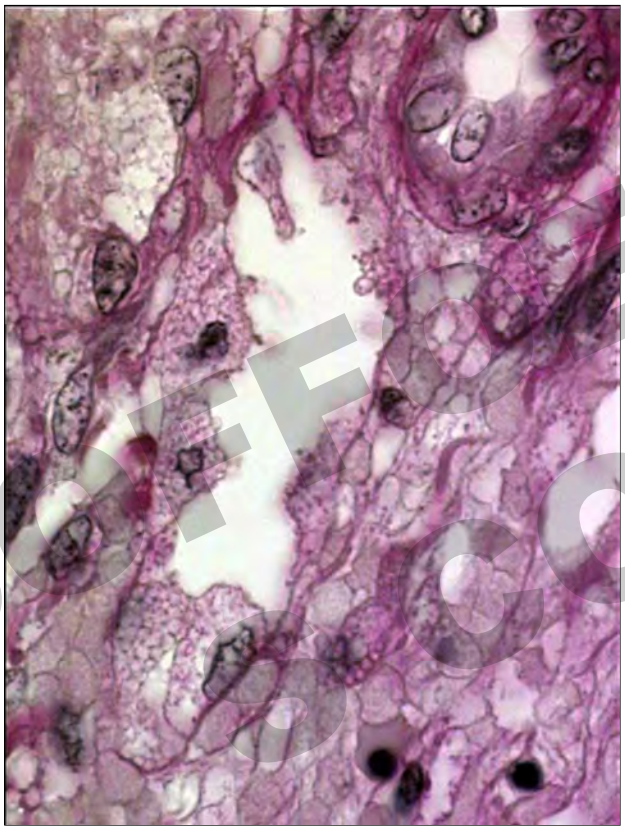



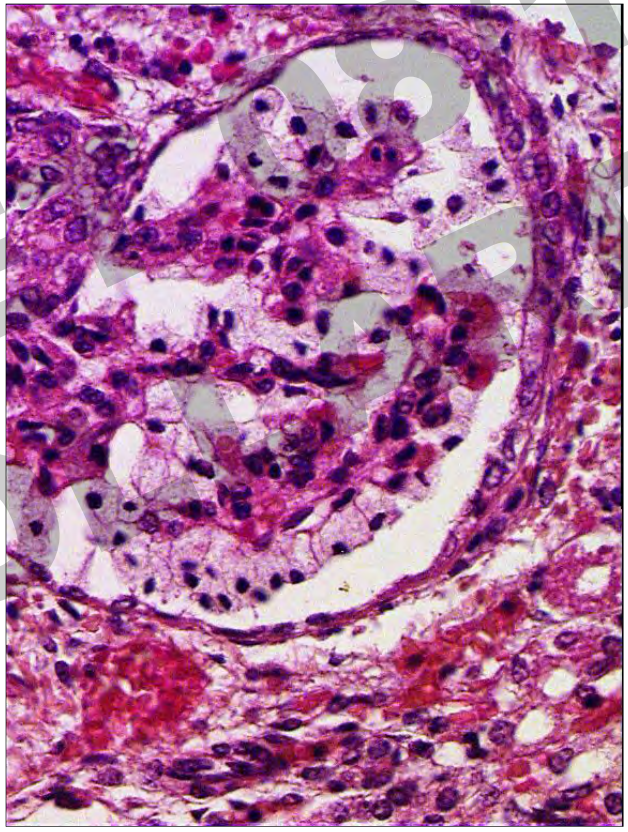

## LSD:

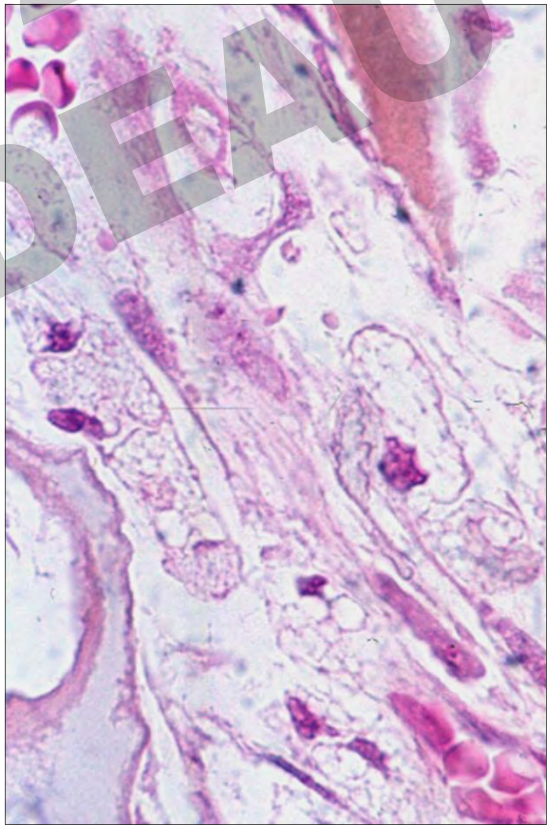
- **Mucolipidosis type II +++**
- **LSD affecting sialic acid metabolism**
- **GM1 gangliosidosis**
- **Mucopolysaccharidoses VII & IVA**

# Examen microscopique oriente vers le type de maladie lysosomale

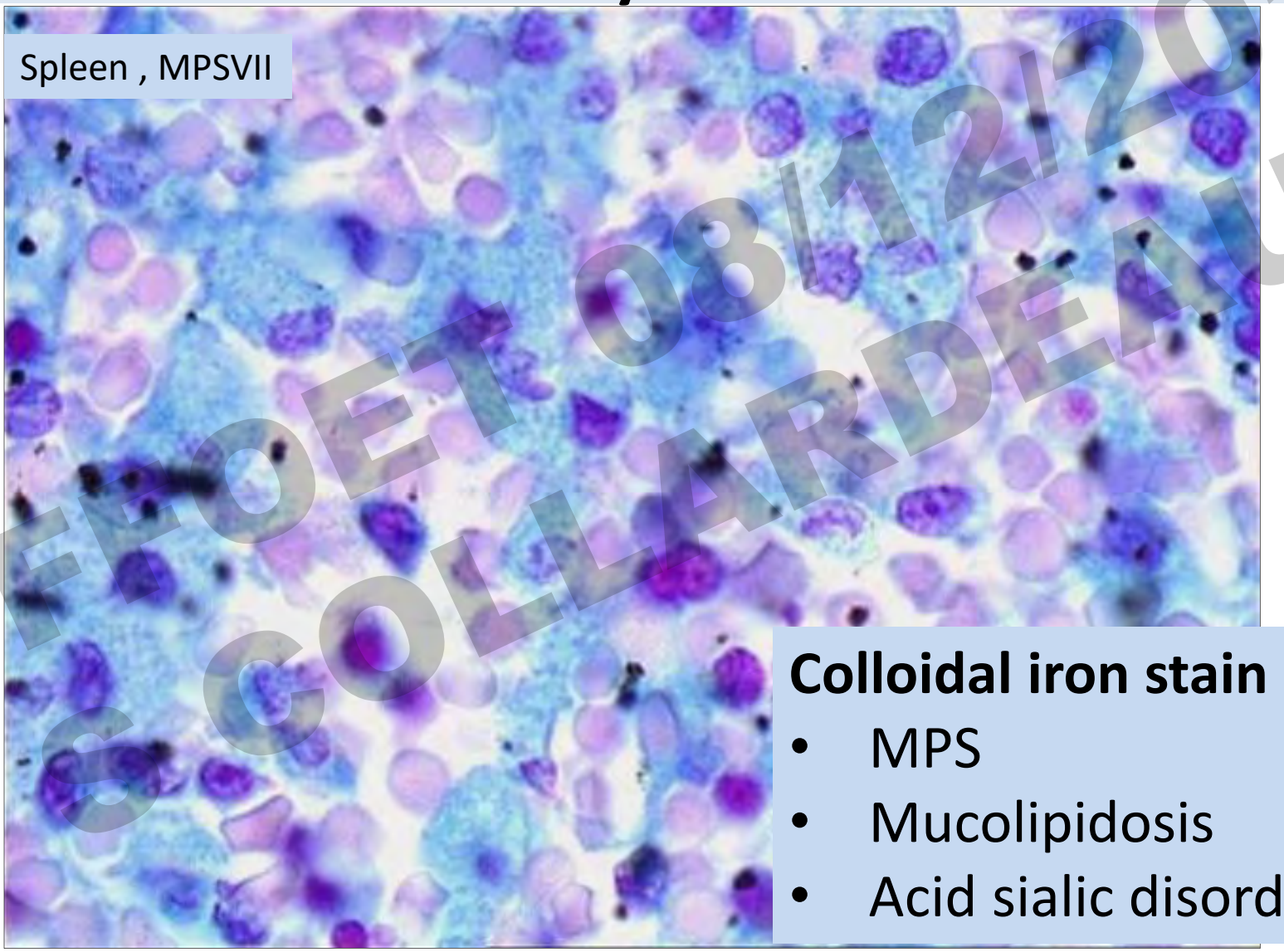
| Endothelial cells overload<br>MPS VII | Podocytes overload<br>Sialic acid disorders<br>Mucolipidosis II | Macrophages overload<br>Metaphyses long bones<br>MPS IV A |
|---|---|---|







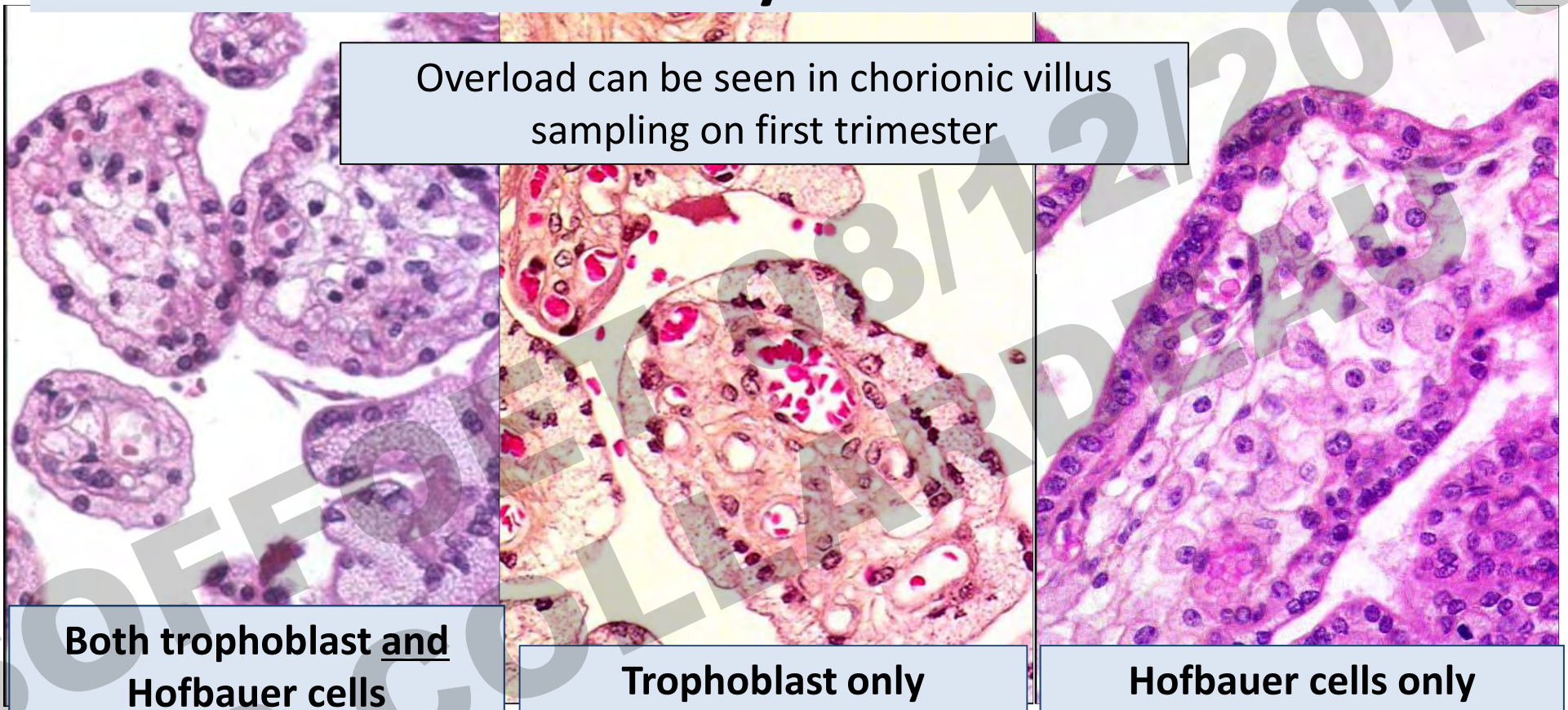
# Examen microscopique oriente vers le type de maladie lysosomale




**Colloidal iron stain + :**

- MPS
- Mucolipidosis
- Acid sialic disorders

# Examen microscopique oriente vers le type de maladie lysosomale



Overload can be seen in chorionic villus sampling on first trimester

**Both trophoblast and Hofbauer cells**

Sialic acid metabolism disorders

GM1 Gangliosidosis

MPS VII (50% cases)

**Trophoblast only**

Mucolipidosis II

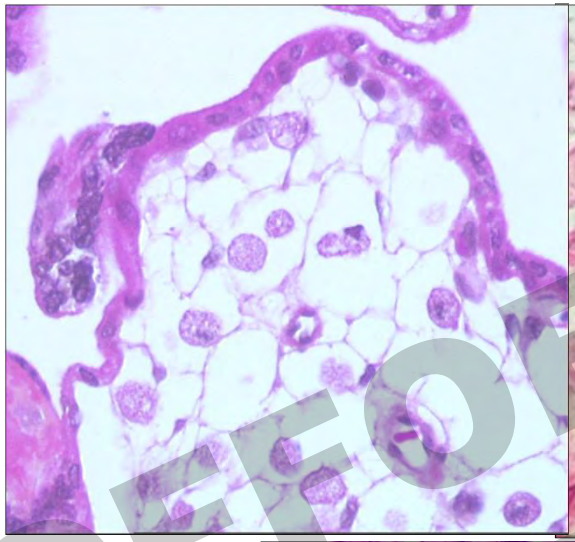
**Hofbauer cells only**

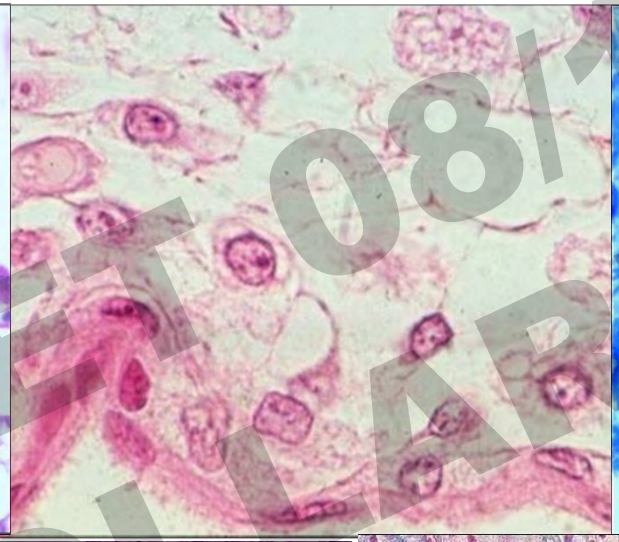
MPS VII (50% cases)

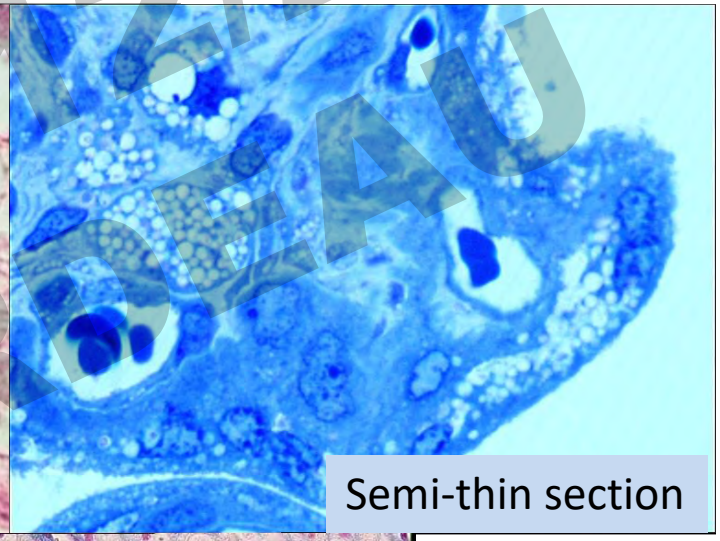
MPS IV

# Examen microscopique oriente vers le type de maladie lysosomale

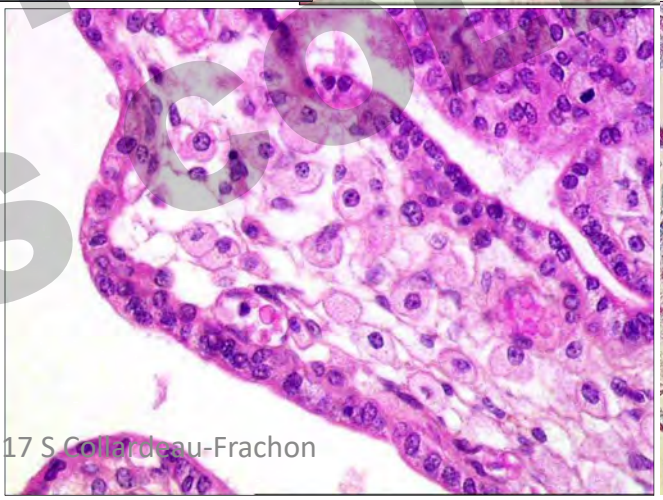
Vacuolization of Hofbauer cells:
hydrops secondary changes or metabolic disorder ?

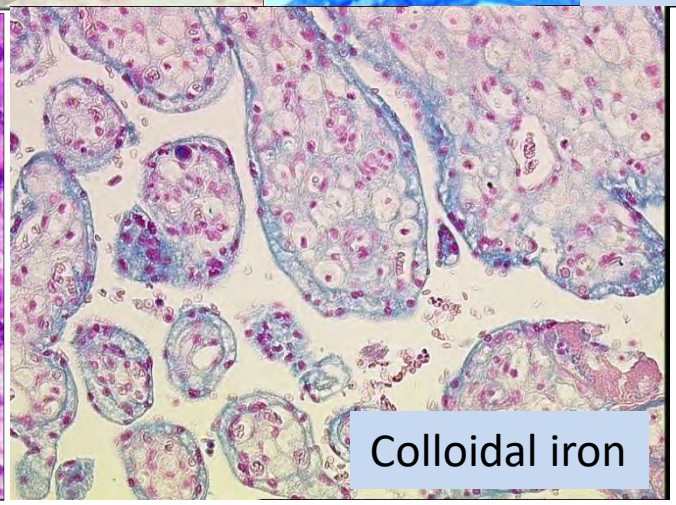






Semi-thin section

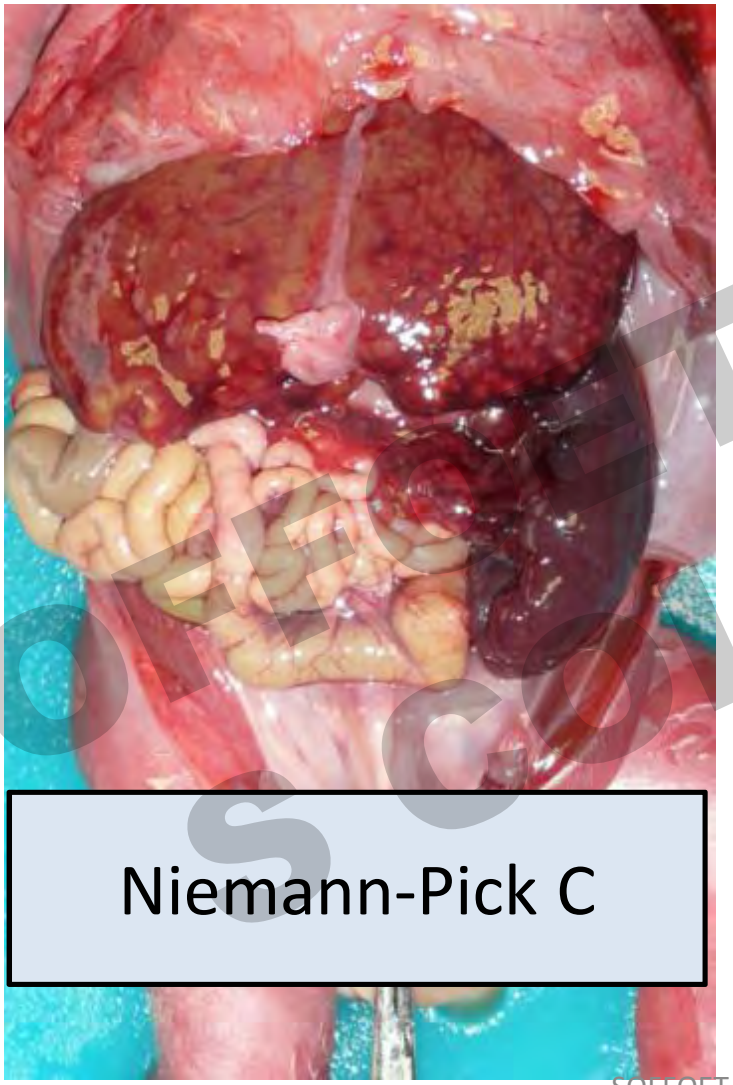




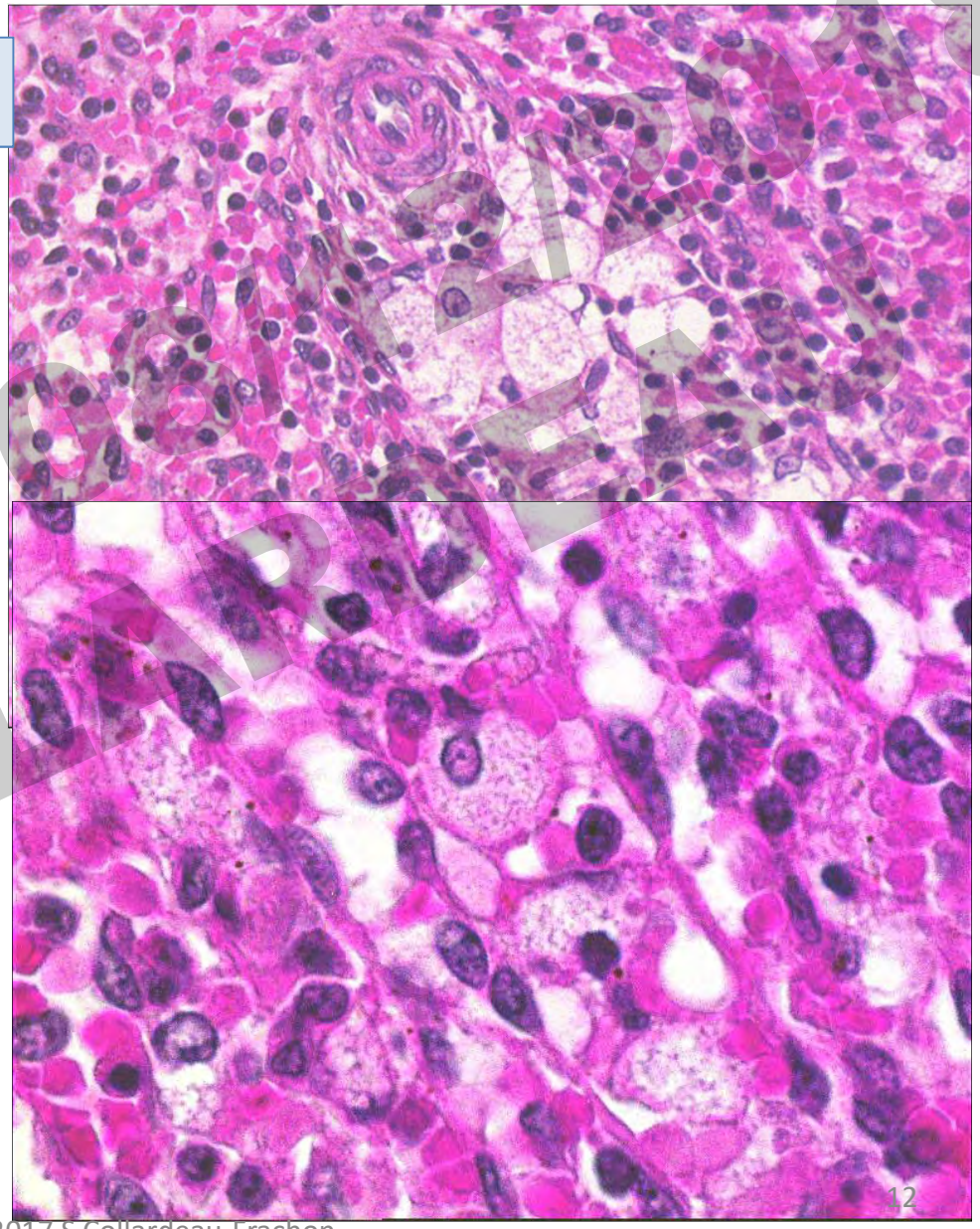
Colloidal iron

# Maladies lysosomales

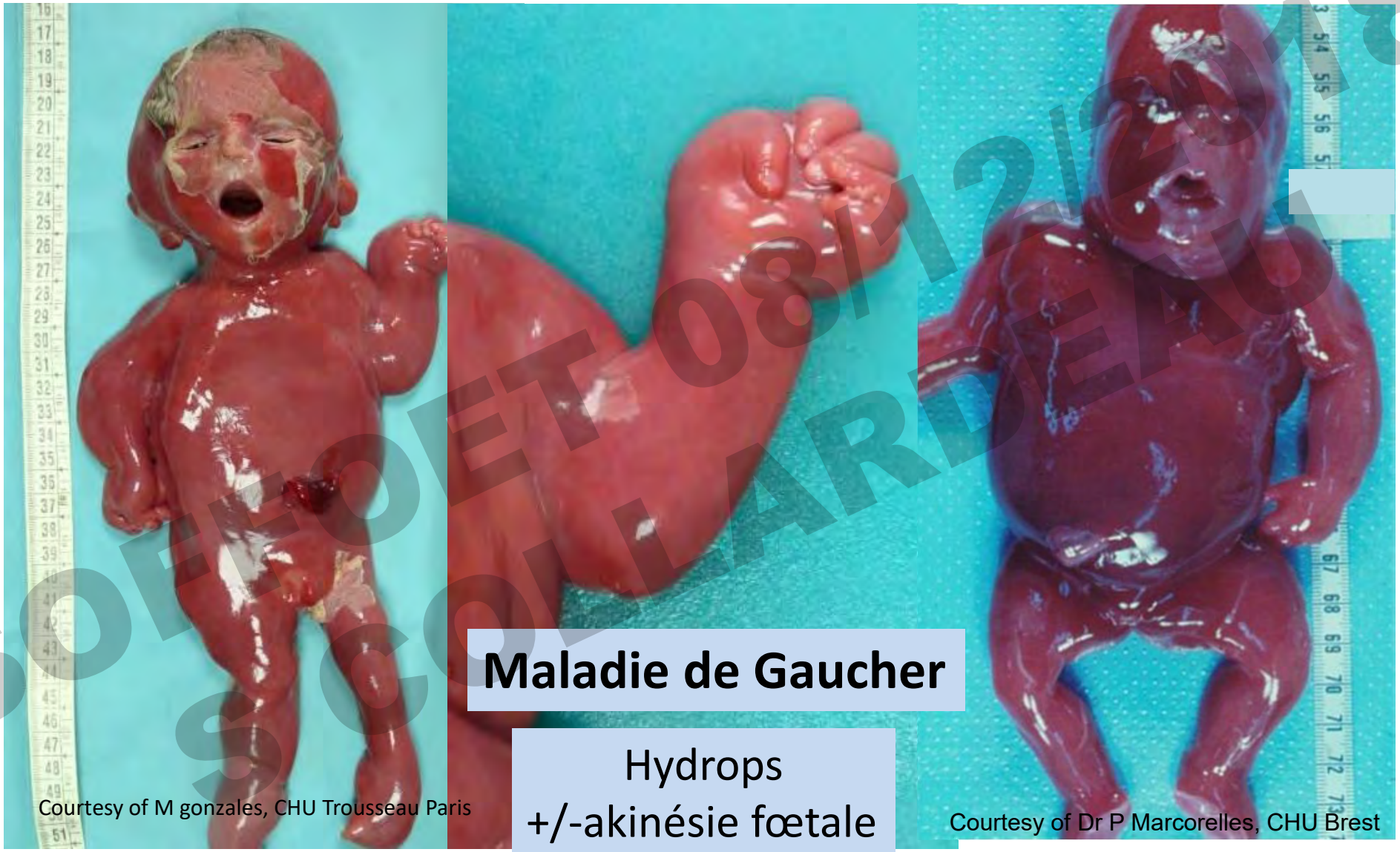
## Importante splénomégalie



Niemann-Pick C



# Maladies lysosomales



Courtesy of M gonzales, CHU Trousseau Paris

Courtesy of Dr P Marcorelles, CHU Brest

## Maladie de Gaucher

Hydrops
+/-akinésie fœtale
+/- ichtyose

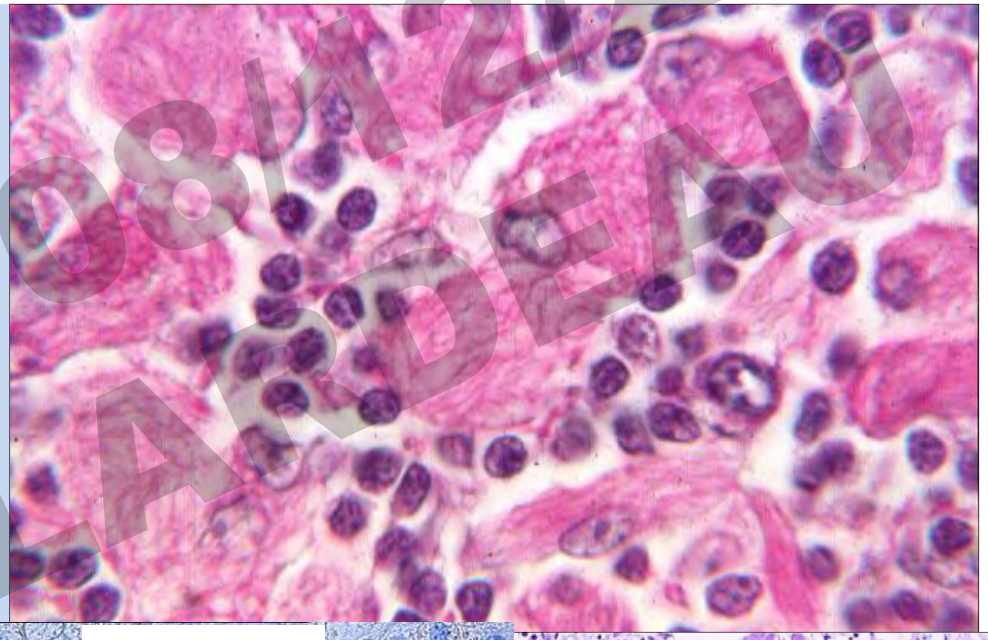
# Maladies lysosomales

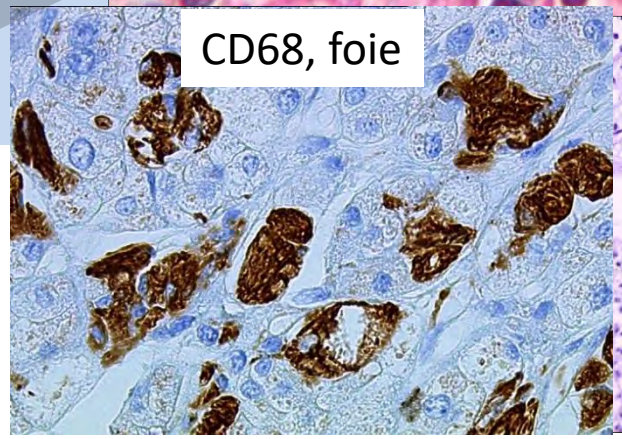
## Maladie de Gaucher

### Examen microscopique: cellules de Gaucher

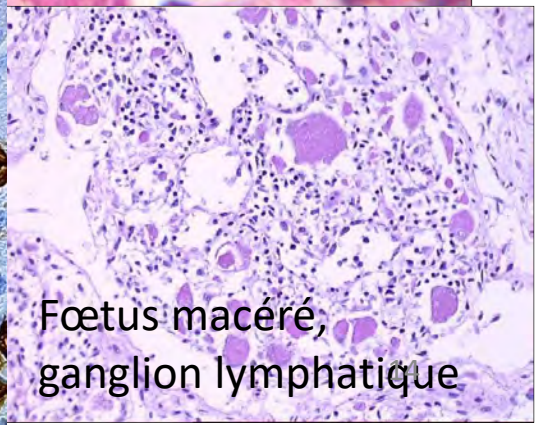
**Macrophages** avec cytoplasme « frippé » du à accumulation de glucosylceramide dans les lysosomes

- **Rate**
- **Foie**
- **Thymus**
- **Ganglions lymphatiques**
- **SNC**
- *(Placenta : dans la lumière des capillaires villositaires)*





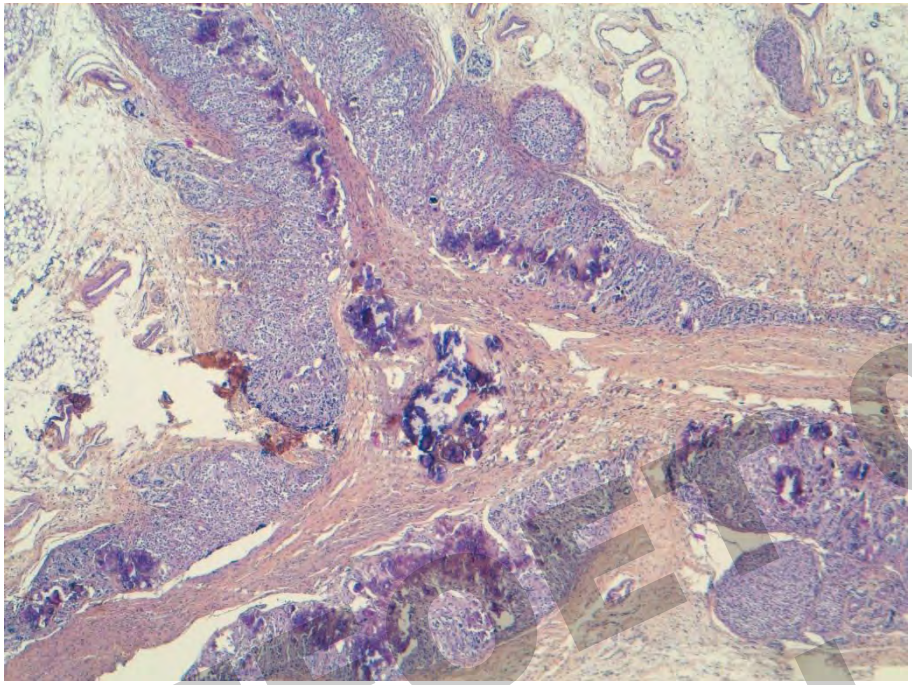
CD68, foie



Fœtus macéré, ganglion lymphatique

**PAS +**
**PAS diastase /amylase +**

# Maladies lysosomales



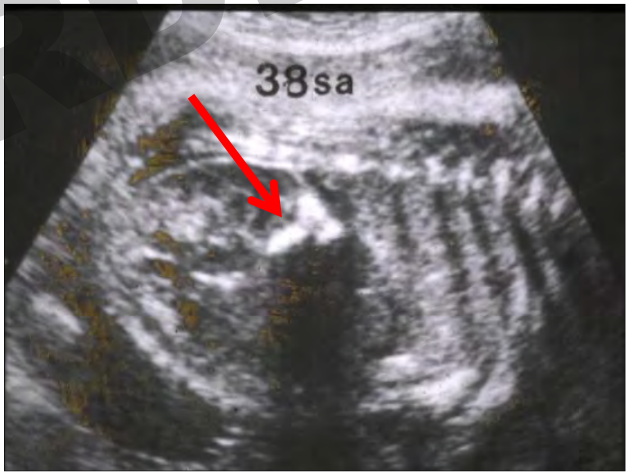
**Wolman disease (LSD)**

cholesterol ester storage disease, acid lipase deficiency

- Hydrops /ascites
- Hepatomegaly (steatosis)

**Bilateral adrenal calcifications**
**→ Wolman disease**

Specific feature – 3nd trimester




*Courtesy of Dr Droullé, Nancy*



Pericleous M, Kelly C, Wang T, Livingstone C, Ala A. Wolman's disease and cholesteryl ester storage disorder: the phenotypic spectrum of lysosomal acid lipase deficiency. Lancet Gastroenterol Hepatol. 2017 Sep;2(9):670-679.

# Maladies lysosomales

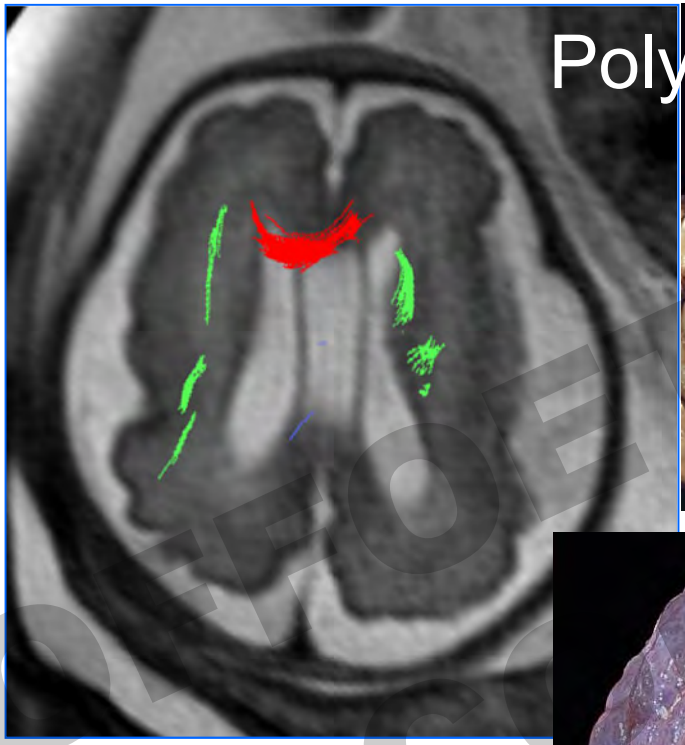
| Disease | Fetus organs | placenta |
|---|---|---|
| MPS VII | Endothelial cells lining lymphatic vessels | Hofbauer cells<br>+/- trophoblast (50% of cases) |
| MPS IV | Metaphyses of long bones | Hofbauer cells |
| LSD affecting sialic acid metabolism | Podocytes<br>Central nervous system<br>Epithelial cells | Trophoblast and Hofbauer cells |
| GM1 gangliosidosis | Central nervous system<br>Epithelial cells | Trophoblast and Hofbauer cells |
| Mucolipidosis type II | Podocytes | Trophoblast |
| Niemann-Pick C | Macrophages in spleen | 0 |
| Gaucher | Gaucher cells in spleen, liver, thymus, lymph nodes, central nervous system | Gaucher cells inside the villous capillaries *(Soma et al, Placenta 2000)* |

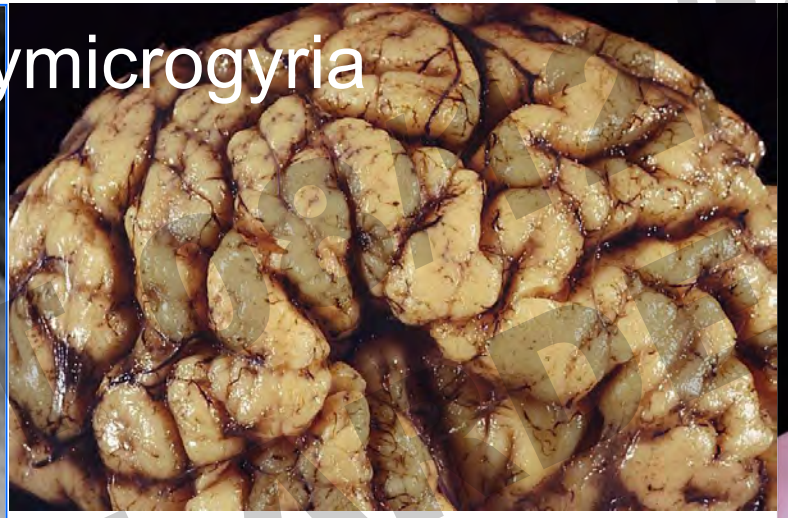
# Maladies peroxisomales

- Zellweger syndrome
- Rhizomelic Chondrodysplasia Punctata: RCDP

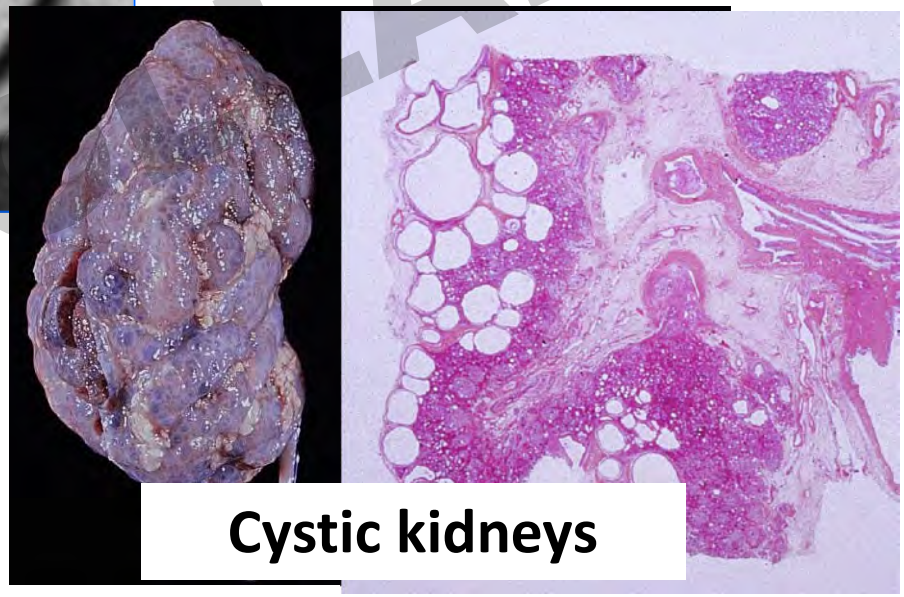
# Zellweger syndrome

## Épiphyse ponctuées: genoux, hanches



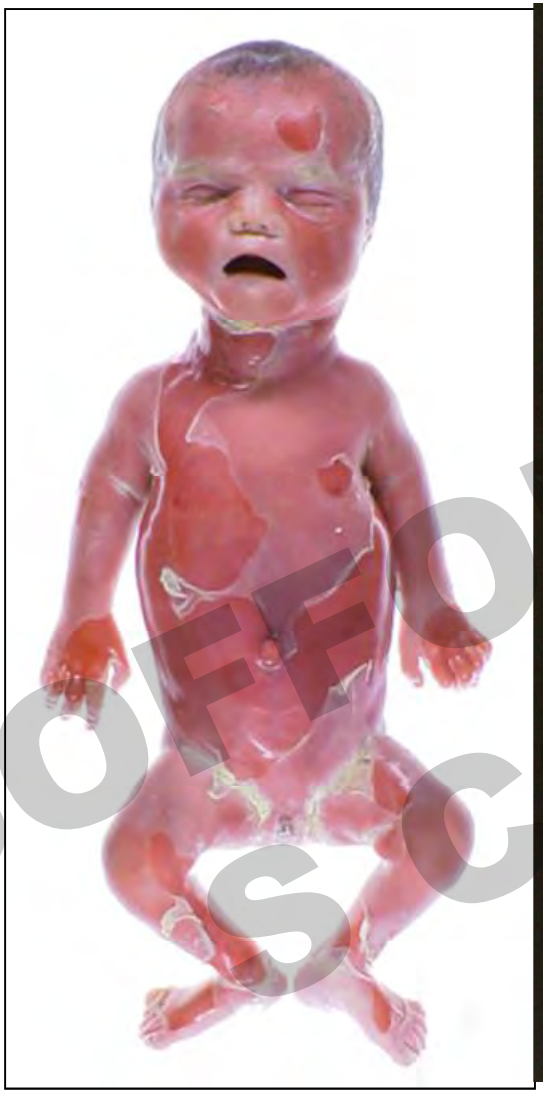
large anterior fontanel, prominent high forehead, broad nasal bridge, micrognathia and redundant neck skin folds

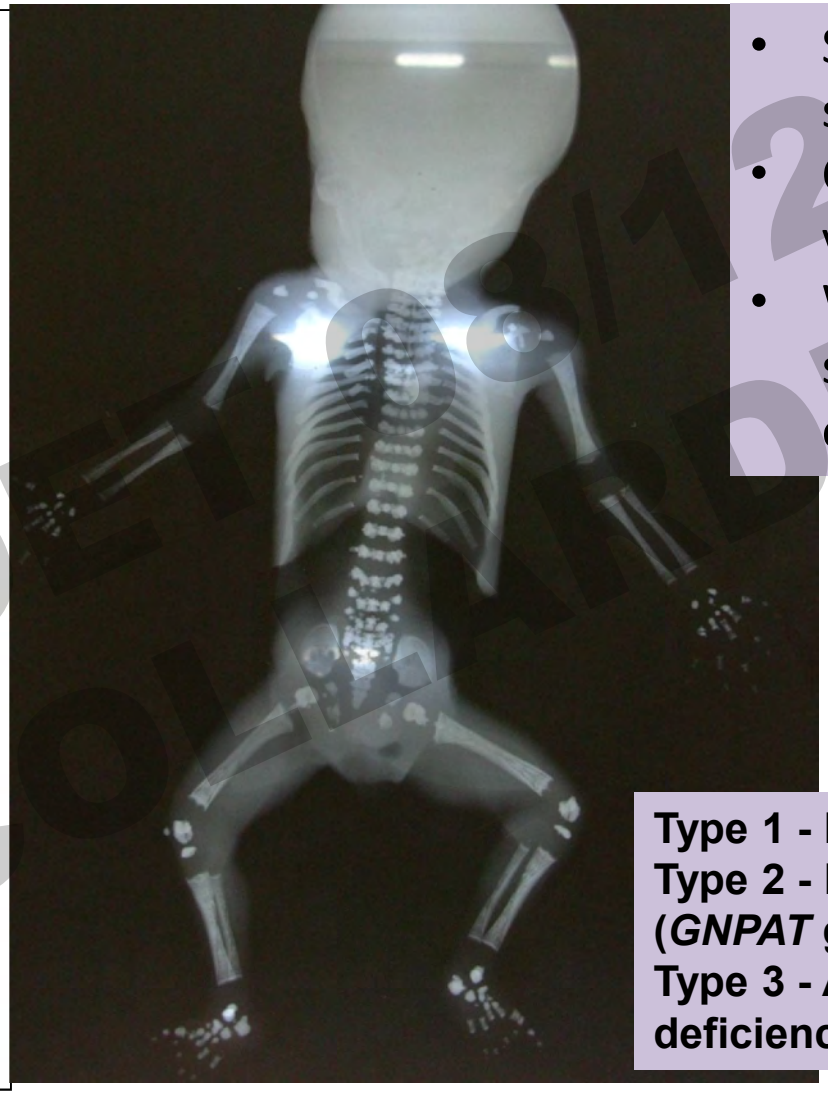


**Cystic kidneys**

Liver:
- Bile duct paucity
- Portal fibrosis
- Hemosiderosis

# Rhizomelic chondrodysplasia punctata
# RCDP





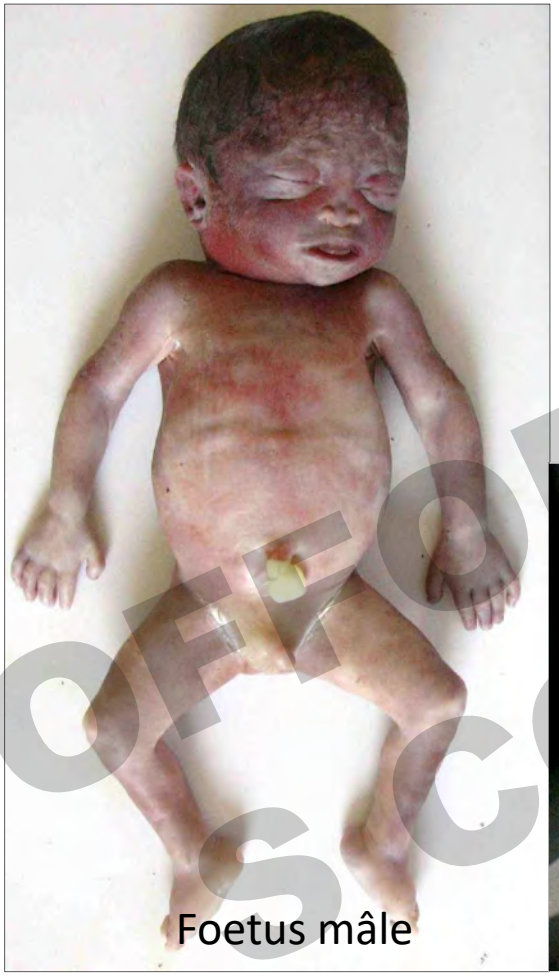
- Severe proximal shortening of limbs
- Coronal clefts of vertebral bodies
- Widespread calcific stippling, may involve extraskeletal tissues

**Type 1 - Mutations *Pex7* gene**
**Type 2 - DHAP-AT deficiency (*GNPAT* gene)**
**Type 3 - Alkyl DHAP synthetase deficiency (*ADHAPS* gene)**

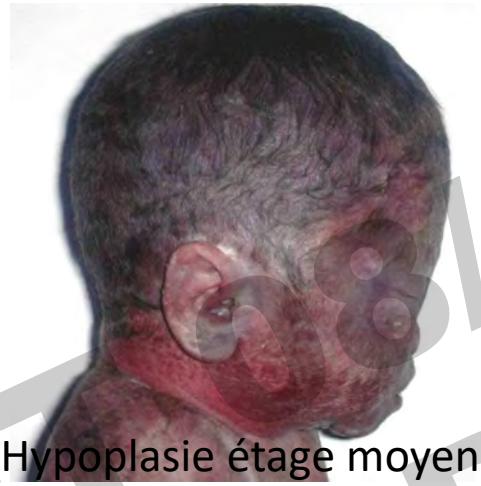
*Courtesy Dr Fabien Guimiot, Robert Debré, Paris*

# Déficit en arylsulfatase E: ARSE

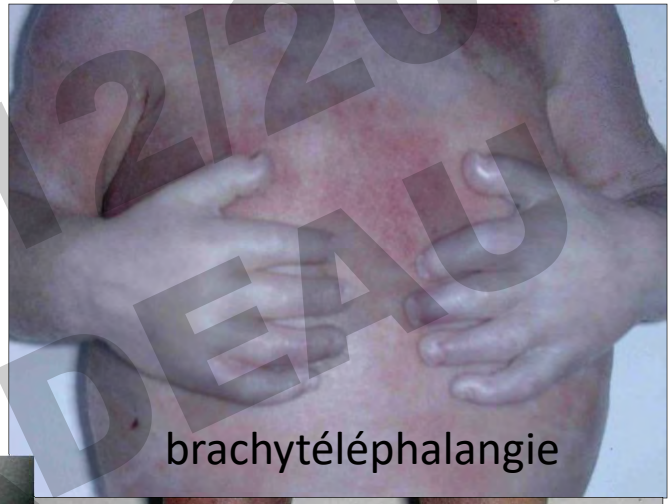
## Chondrodysplasie ponctuée brachytéléphalangique (CPDX1)



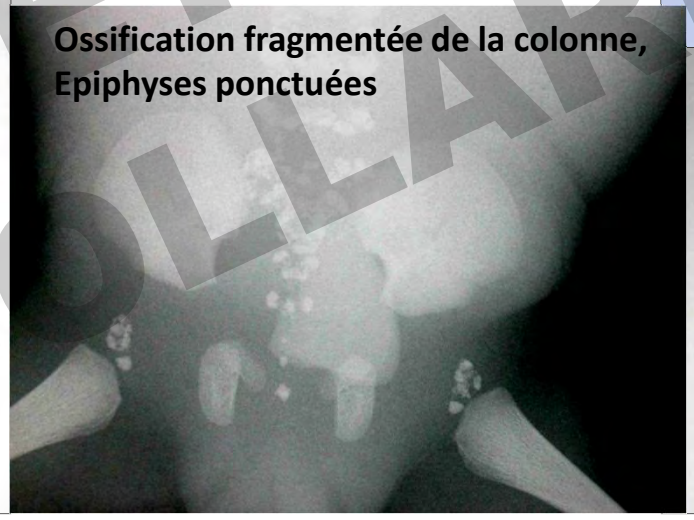
Foetus mâle



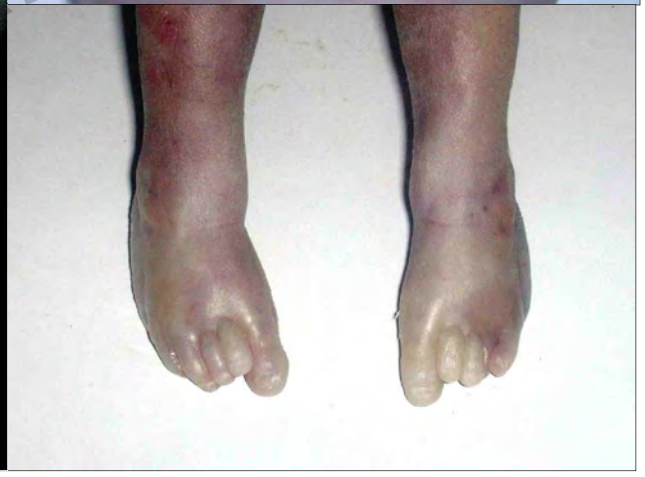
Hypoplasie étage moyen



brachytéléphalangie



**Ossification fragmentée de la colonne, Epiphyses ponctuées**

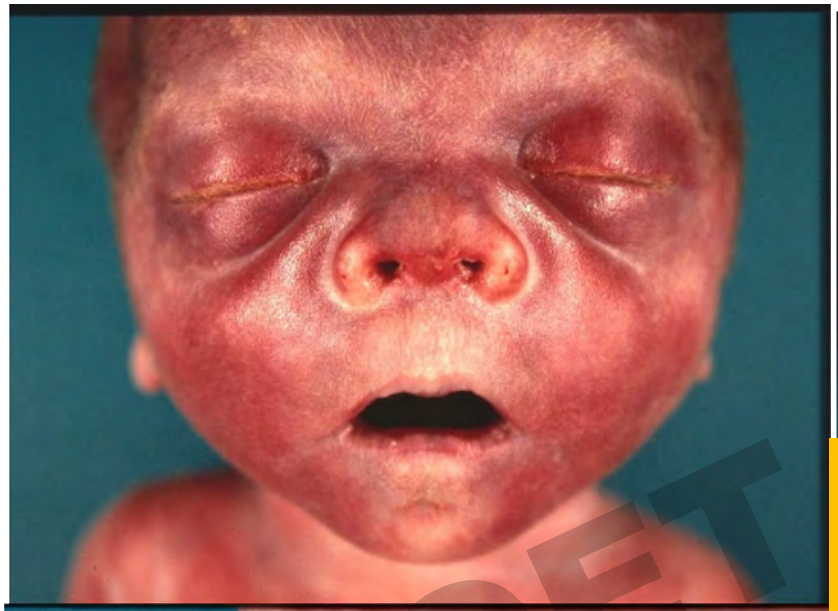


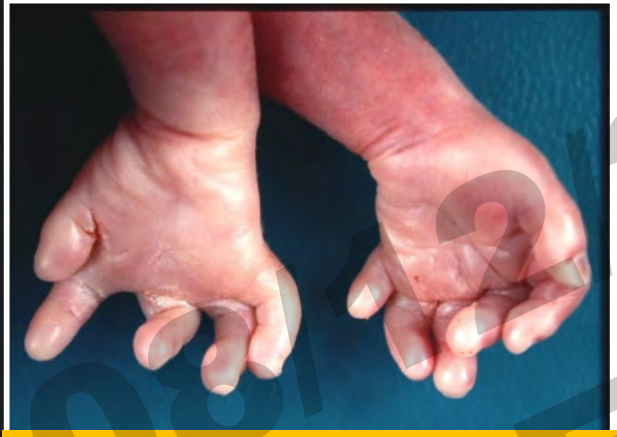
récessive liée à l'X: gène ARSE (Golgi enzyme)

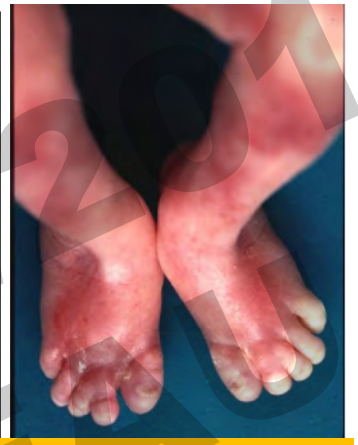
# Cholestérolopathies

- Smith-Lemli-Opitz
- Lathosterolosis
- Desmosterolosis
- Conradi-Hünermann (CPDX2)
- CHILD syndrome
- Antley Bixler syndrome
- Greenberg dysplasia

# Smith-Lemli-Opitz



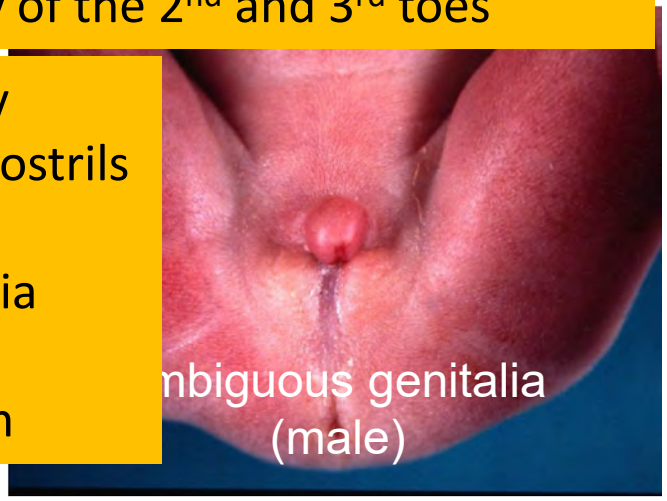




- Growth restriction
- Polydactyly of the hands
- proximally placed thumbs
- Syndactyly of the 2nd and 3rd toes

*Courtesy of Dr M Gonzales, Hop Trousseau, Paris*

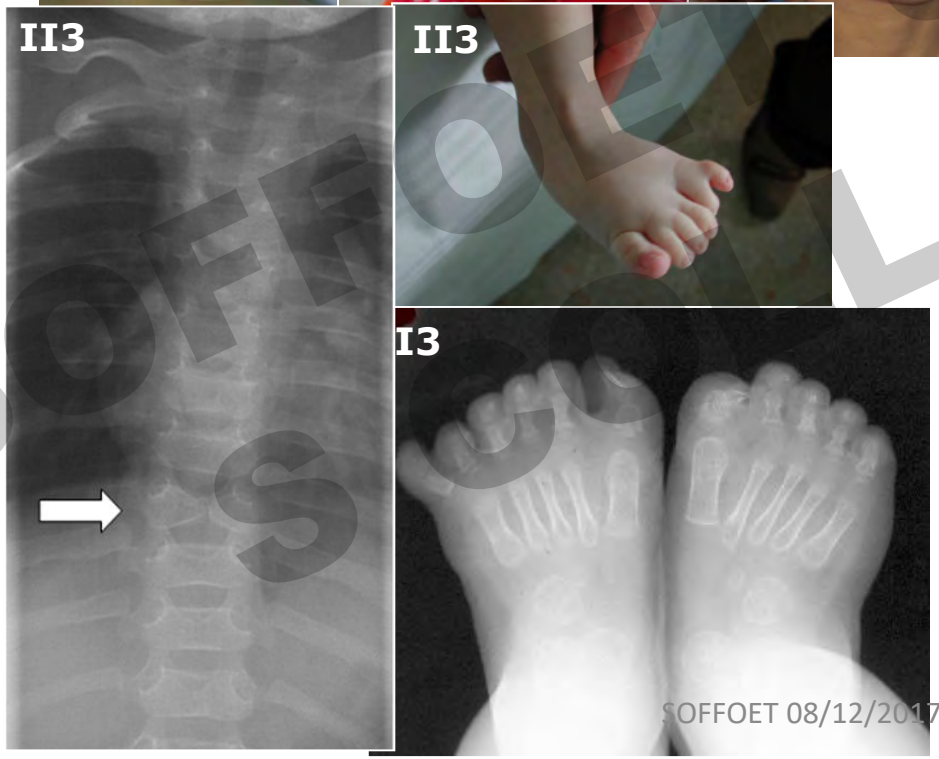
Microcephaly
Anteverted nostrils
Small chin
&micrognathia
Low set ears
High philtrum

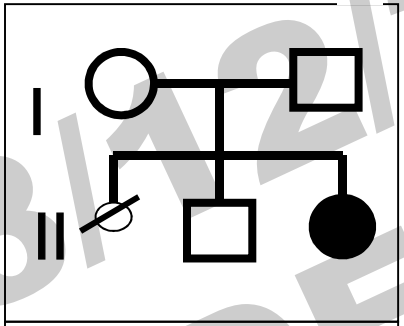


mbiguous genitalia
(male)

# Lathostérolose: tableau de SLO atypique

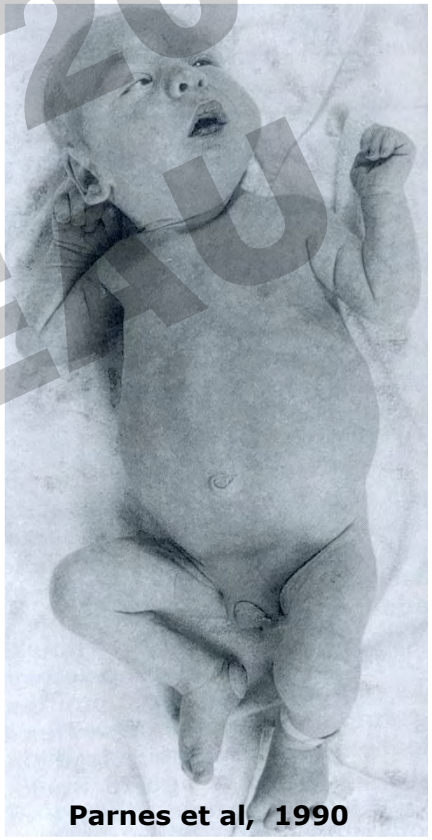
**Inheritance: Autosomal recessive**
**Aetiology: sterol-C5-desaturase (*SC5DL*) gene :déficit en 3β-hydroxysteroid-Δ5-desaturase (SC5D)**


**II1:**
- **microcephaly**
- **hexadactyly of four limbs**
- **clubfeet**
- **lumbosacral meningocele**

vacuolisations cytoplasmiques lysosomales



**Parnes et al, 1990**

JIMD Reports
DOI 10.1007/8904_2013_255

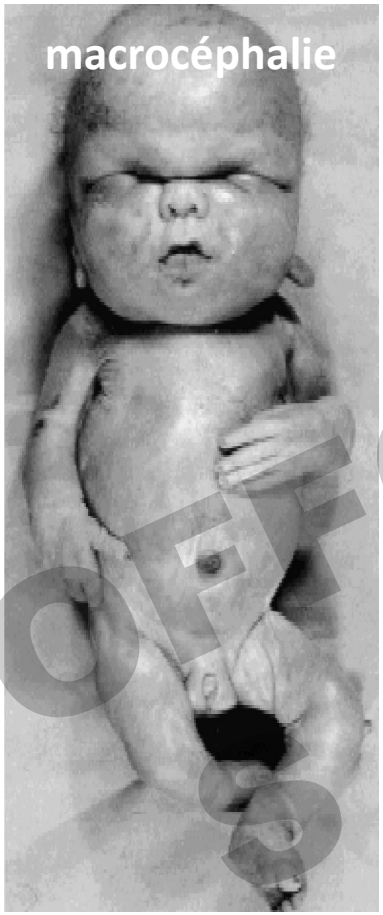
CASE REPORT

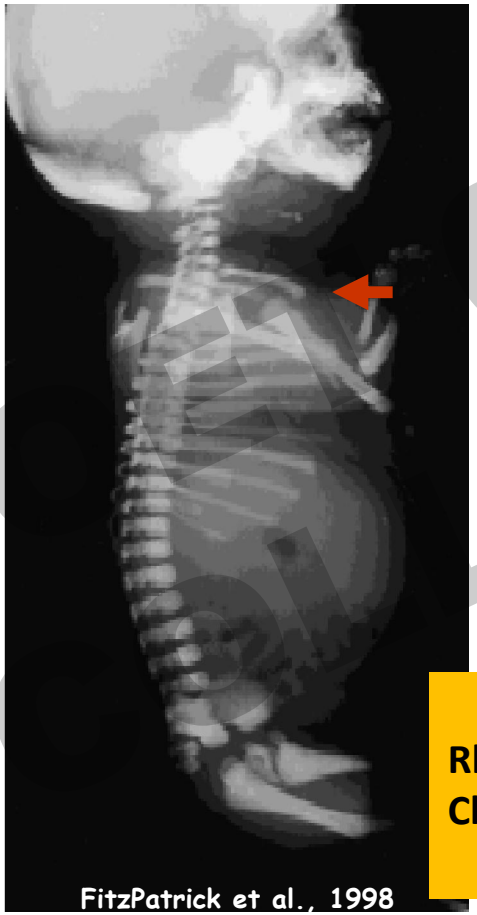
**Lathosterolosis: A Disorder of Cholesterol Biosynthesis Resembling Smith-Lemli-Opitz Syndrome**

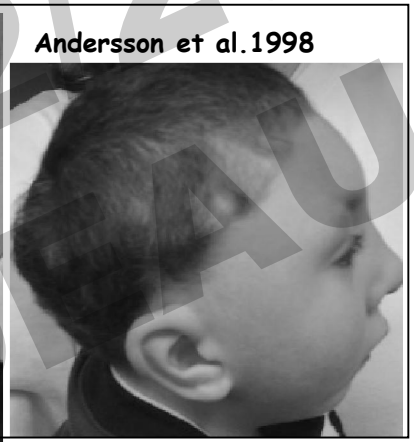
A.C.C. Ho · C.W. Fung · T.S. Siu · O.C.K. Ma · C.W. Lam · S. Tam · V.C.N. Wong

# Desmostérolose

**Inheritence: Autosomal recessive**
**Aetiology: 3 β-hydroxysterol Δ24-reductase (DHCR24 gene)**



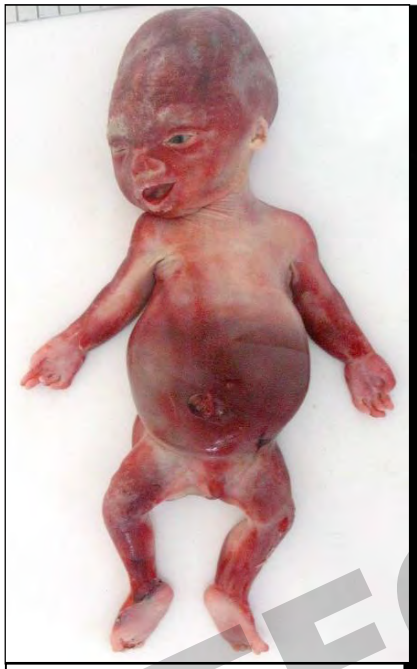



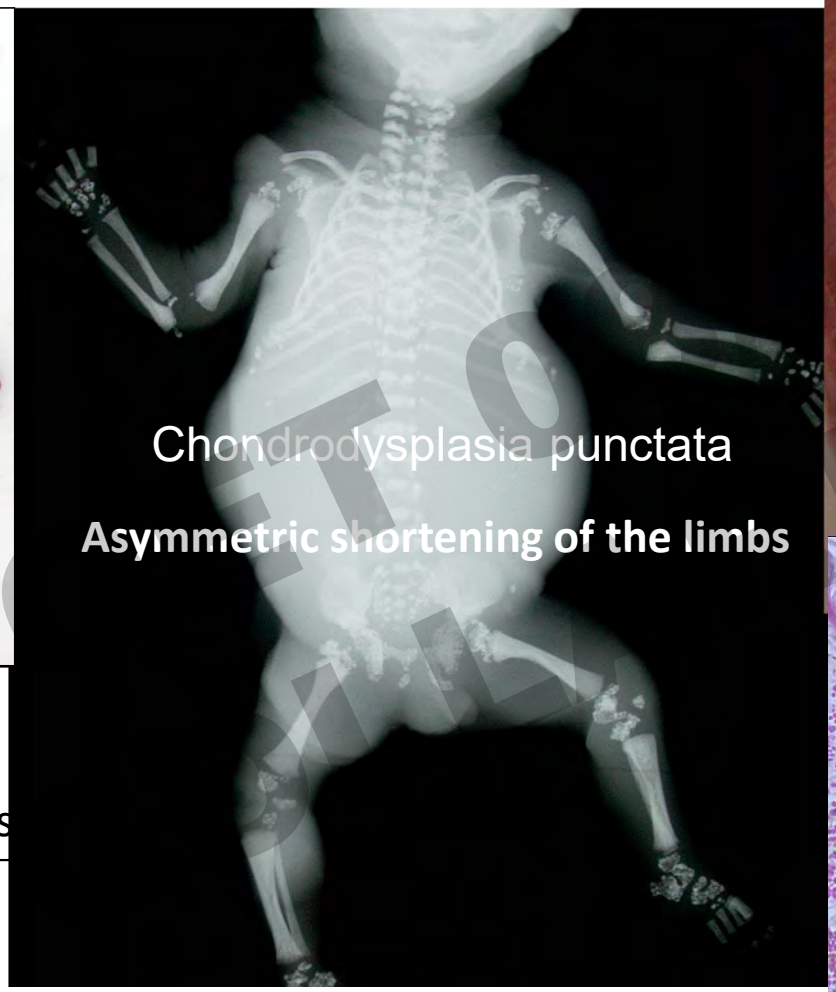

nodules gingivaux et fente palatine, ambiguïté des OGE, atteinte du SNC, **microcéphalie** majeure, ostéosclérose (1/9)

**Skeletal involvement:**
**Rhizomelic limbs shortening and osteosclerosis (1/2)**
**Clubfoot/ fingers contracture (1/2)**

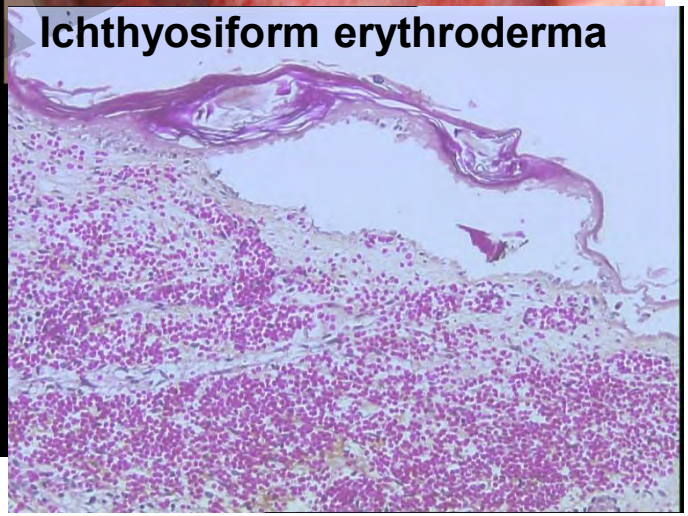
# X-linked dominant chondrodysplasia punctata-2 (CPDX2) : Conradi-Hünermann-Happle syndrome



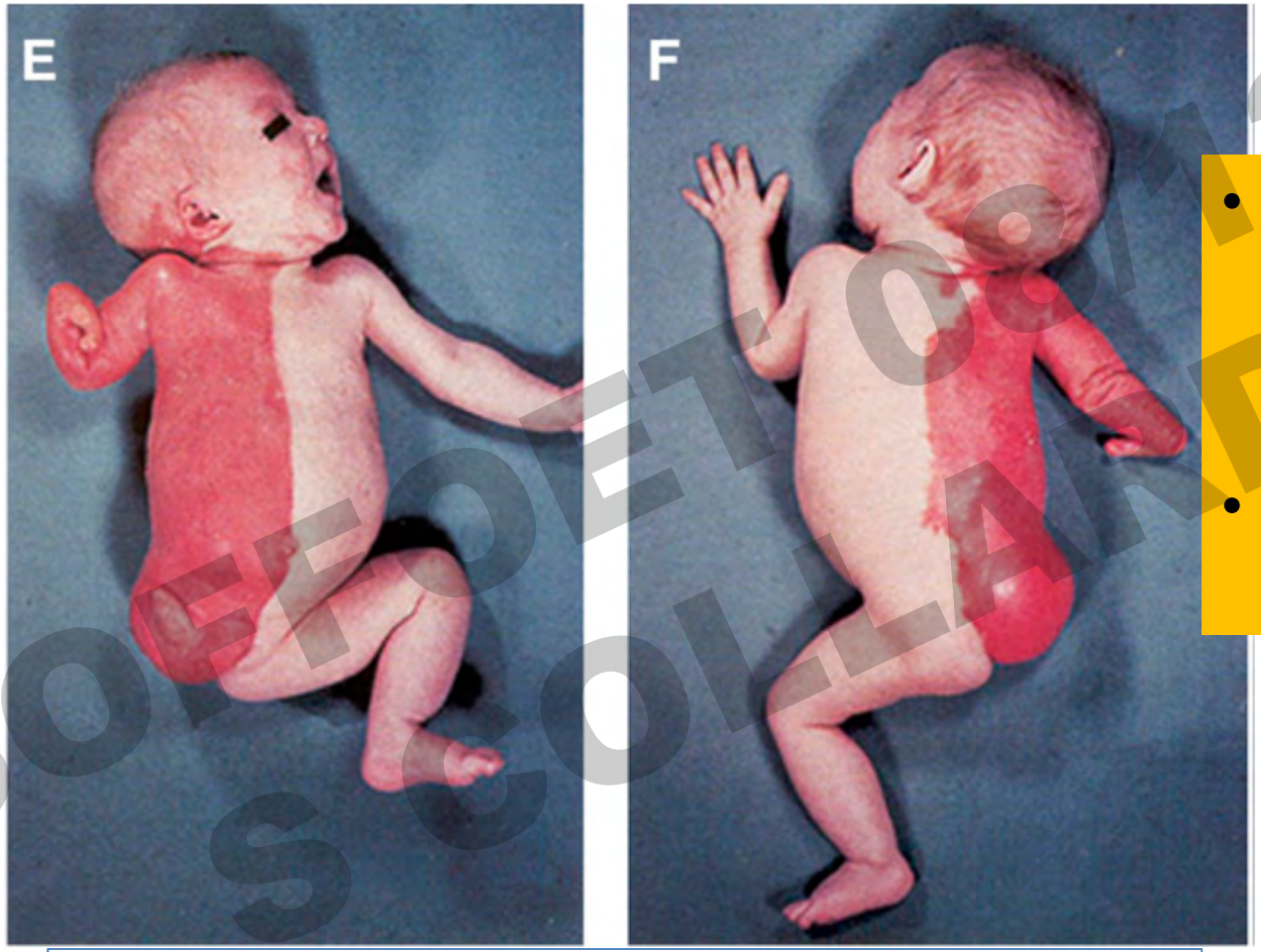
TOP 23GW for HF
+short femurs
+stippled epiphyses







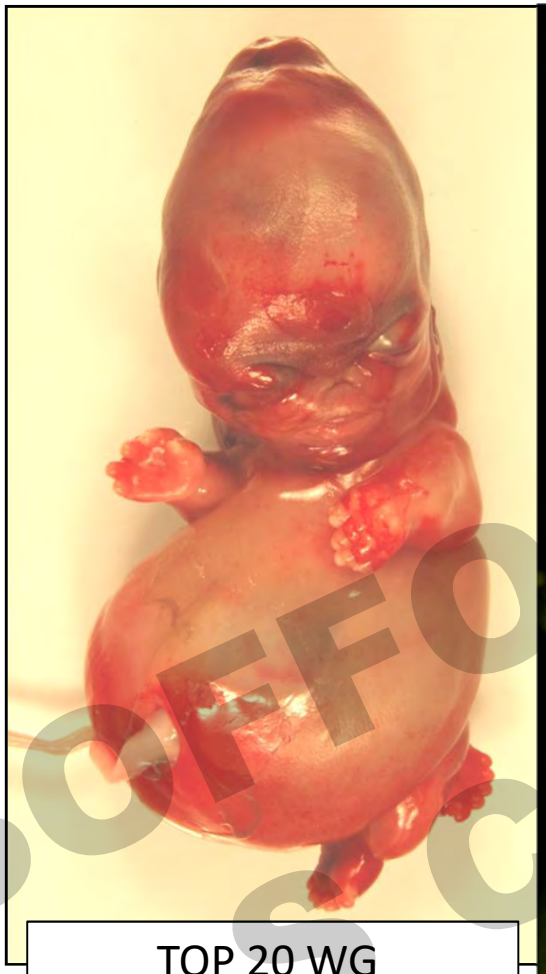
# **C**ongenital **H**emidysplasia with **I**chthyosiform naevus and **L**imb **D**efects **(CHILD)**




- Unilateral, sharply demarcated, erythematous, ichthyosiform nevus,
- and ipsilateral limb reduction

*Malformation syndromes caused by disorders of cholesterol synthesis. Forbes D. Porter, Gail E. Herman. J Lipid Res. 2011; 52(1): 6–34.*

# Greenberg dysplasia



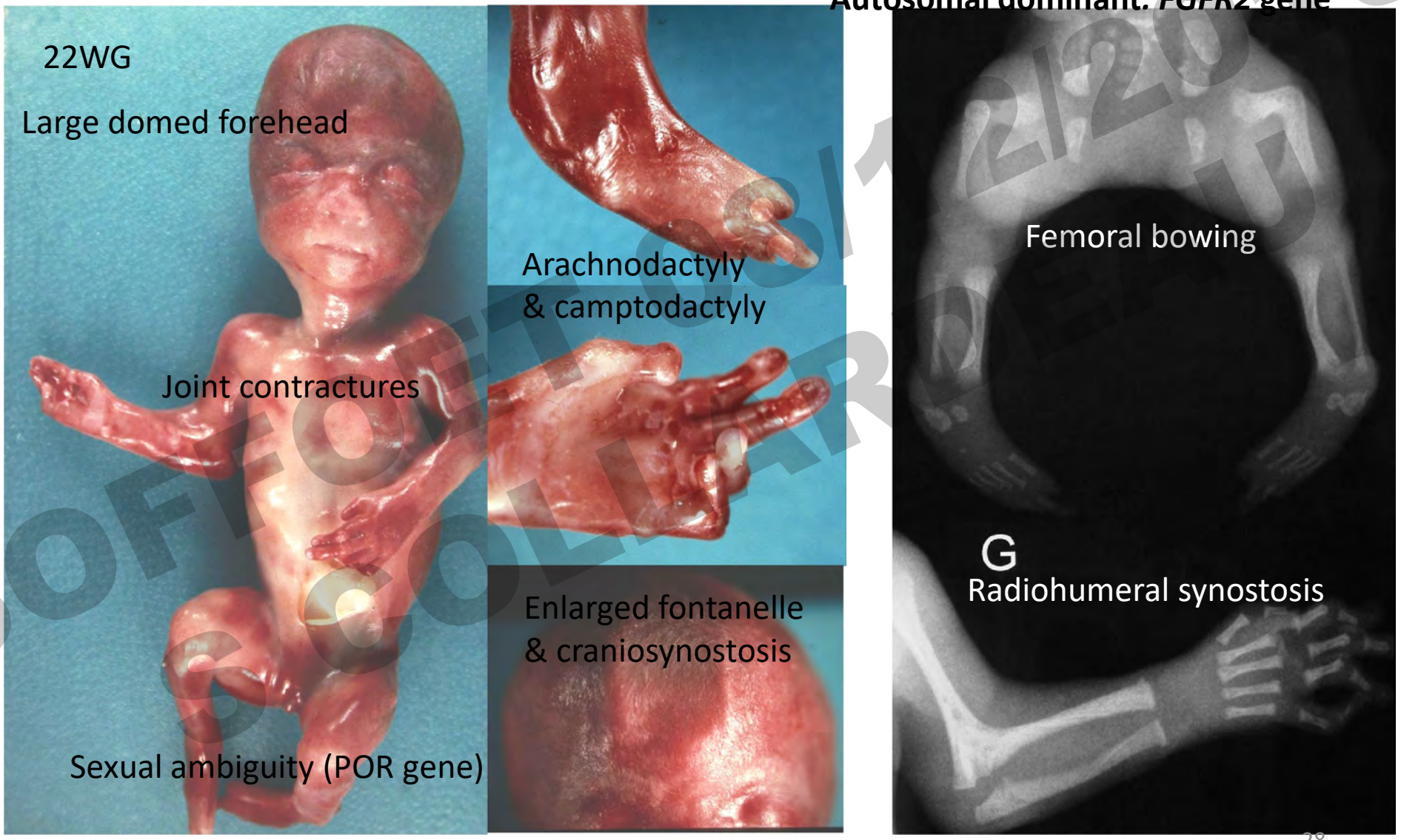
TOP 20 WG

for **fetal hydrops**

and **severe micromelia**

# Antley-Bixler syndrome

**Autosomal recessive: *POR* gene**
**Autosomal dominant: *FGFR2* gene**



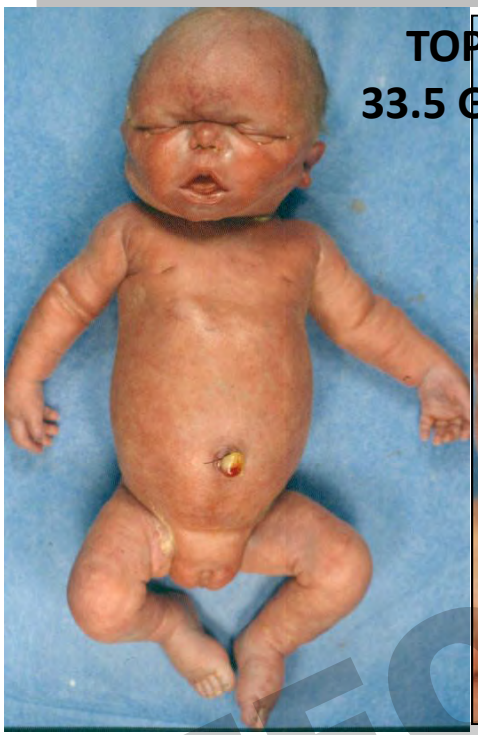

*Courtesy of Dr M Gonzales, Hop Trousseau, Paris*

# Congenital Disorders of Glycosylation: CDG

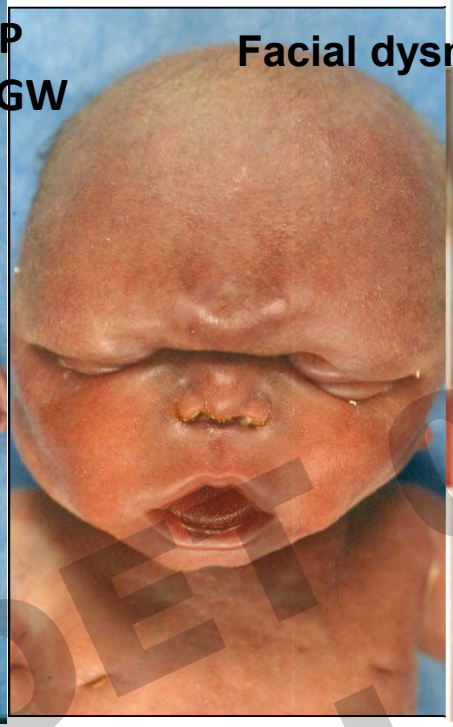
- N-CDG
- O-CDG : voir topo suivant

| | stippled epiphyses | shortening of the limbs | craniosynostosis | anomlies of the extremities | joint contractures | IUGR | hydrops | midface hypoplasia hypertrophic cardiomyopathy | cystic kidneys | hepatomegaly | liver hemosiderosis | liver bil ducts anomalies | microcephaly | corpus callosum anomalies | posterior fossa anomalies |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PMM2-CDG | | | | | | X | | | X | | X | X | | | X |
| ALG3-CDG | X | X | | | X | X | | | | X | | X | | X | X |
| ALG12-CDG | | X | | X | | | X | X | X | | | | | | X |
| SLC39A8 deficiency | | X | X | X | | X | | | | | | | X | | X |
| COG7-CDG | | | | X | | X | | | | | | | X | X | |

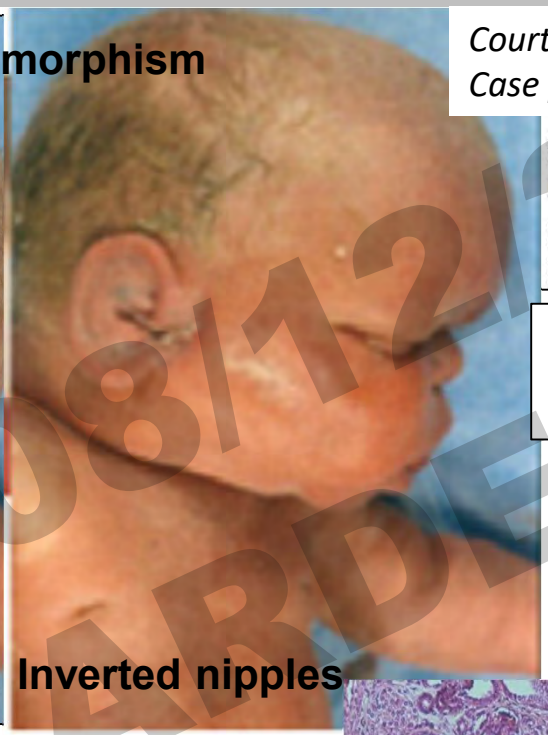
# *PMM2*-CDG (CDG Ia)



TOP
33.5 GW

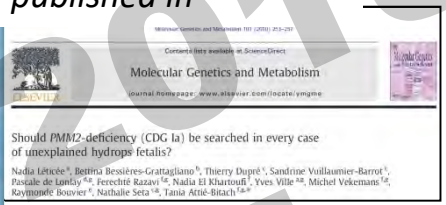


Facial dysmorphism



Inverted nipples

*Courtesy of Dr B Bessières,*
*Case published in*

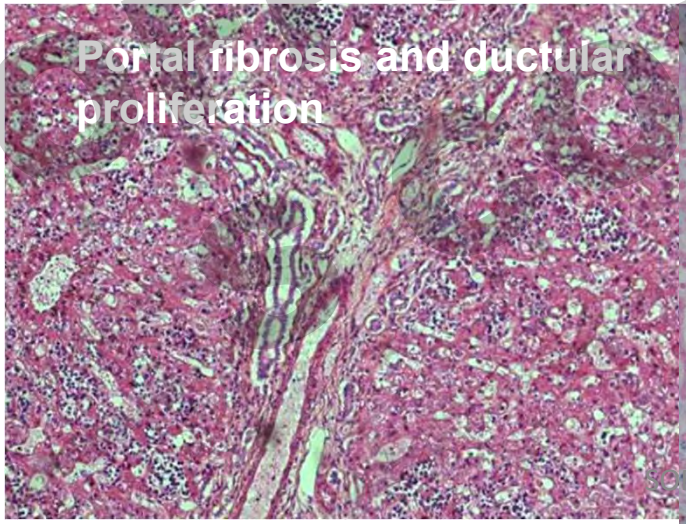


Molecular Genetics and Metabolism

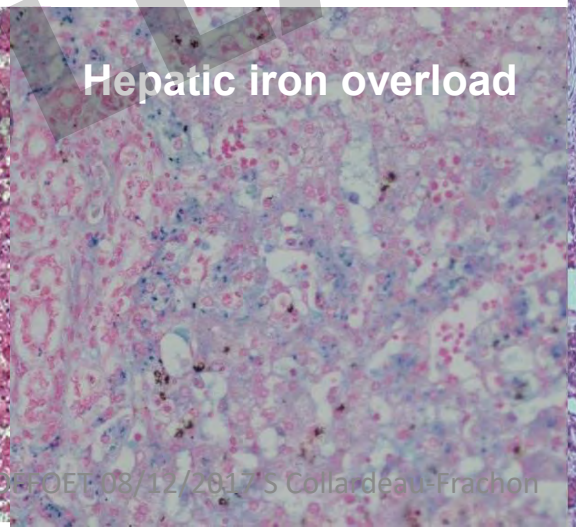
Should *PMM2*-deficiency (CDG Ia) be searched in every case of unexplained hydrops fetalis?

midface hypoplasia
frontal bossing

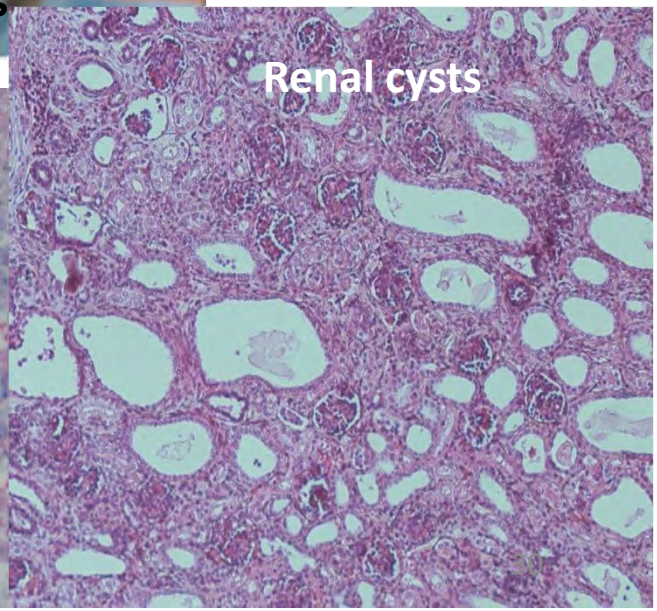
*abnormal fat distribution, fat pads*



Portal fibrosis and ductular proliferation

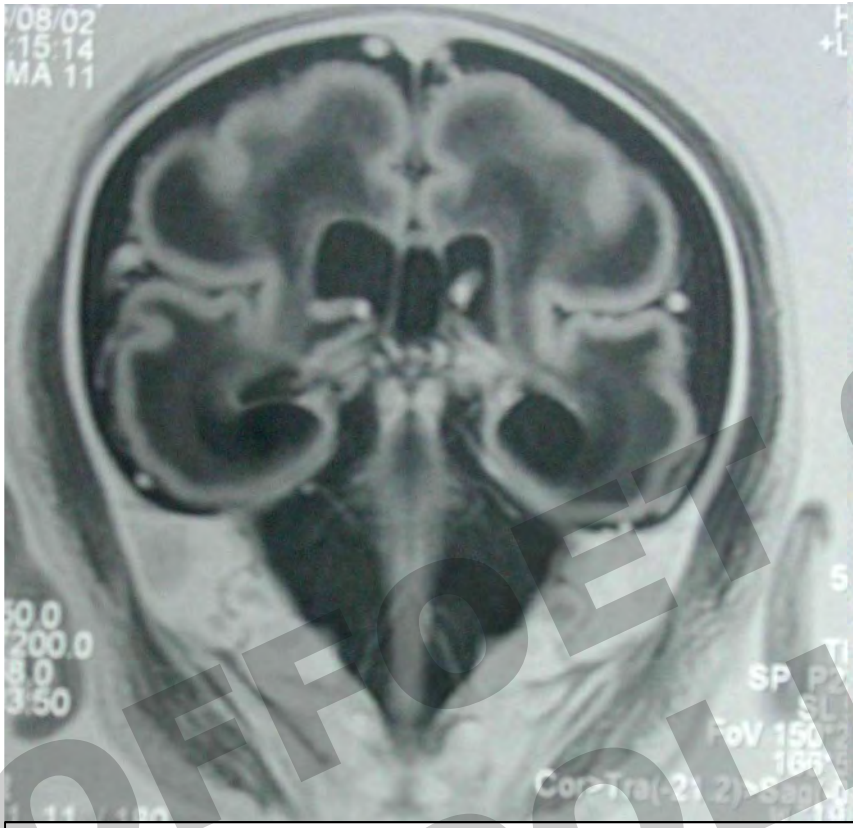


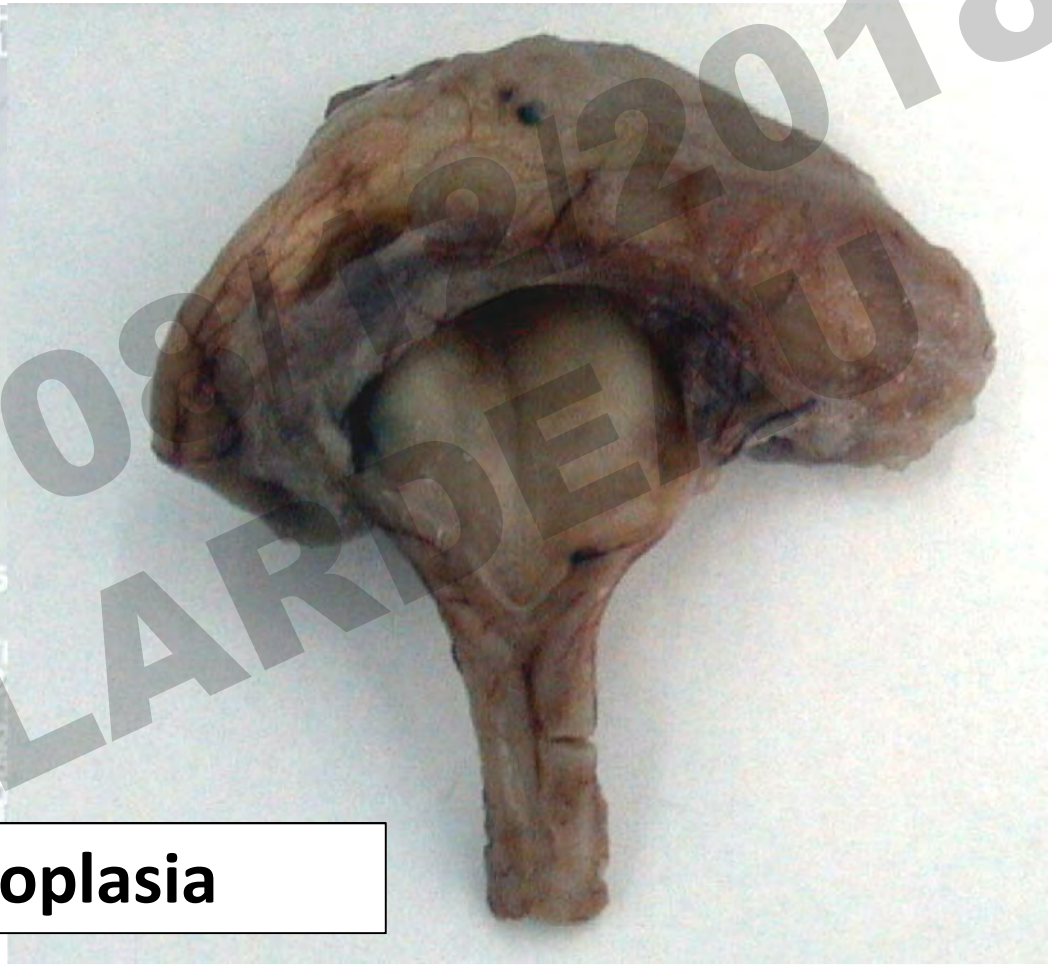
Hepatic iron overload



Renal cysts

# ***PMM2*-CDG** (CDG Ia)





**Ponto-cerebellar hypoplasia**

**Congenital disorders of N-glycosylation (CDG)**
**Especially PMM2-CDG (CDG Ia) the most frequent**
PhosphoMannoMutase 2 deficiency ( PMM2 gene -16p13)

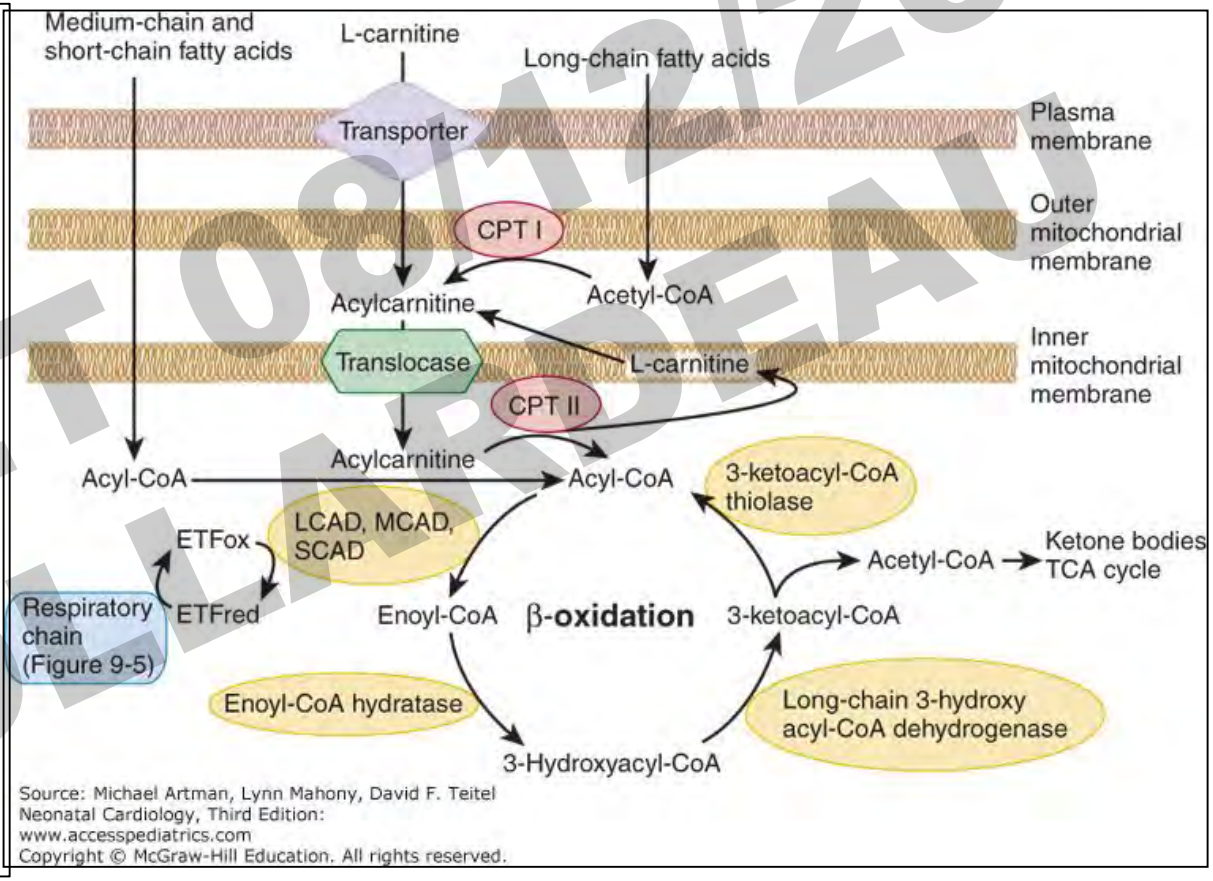
# Déficit de l'oxydation des acides gras

**Atteint les organes qui utilisent la voie de catabolisme des lipides : muscles, cœur, foie, reins (tubes proximaux)**

**Conséquences :**

**Surcharge lipidique**

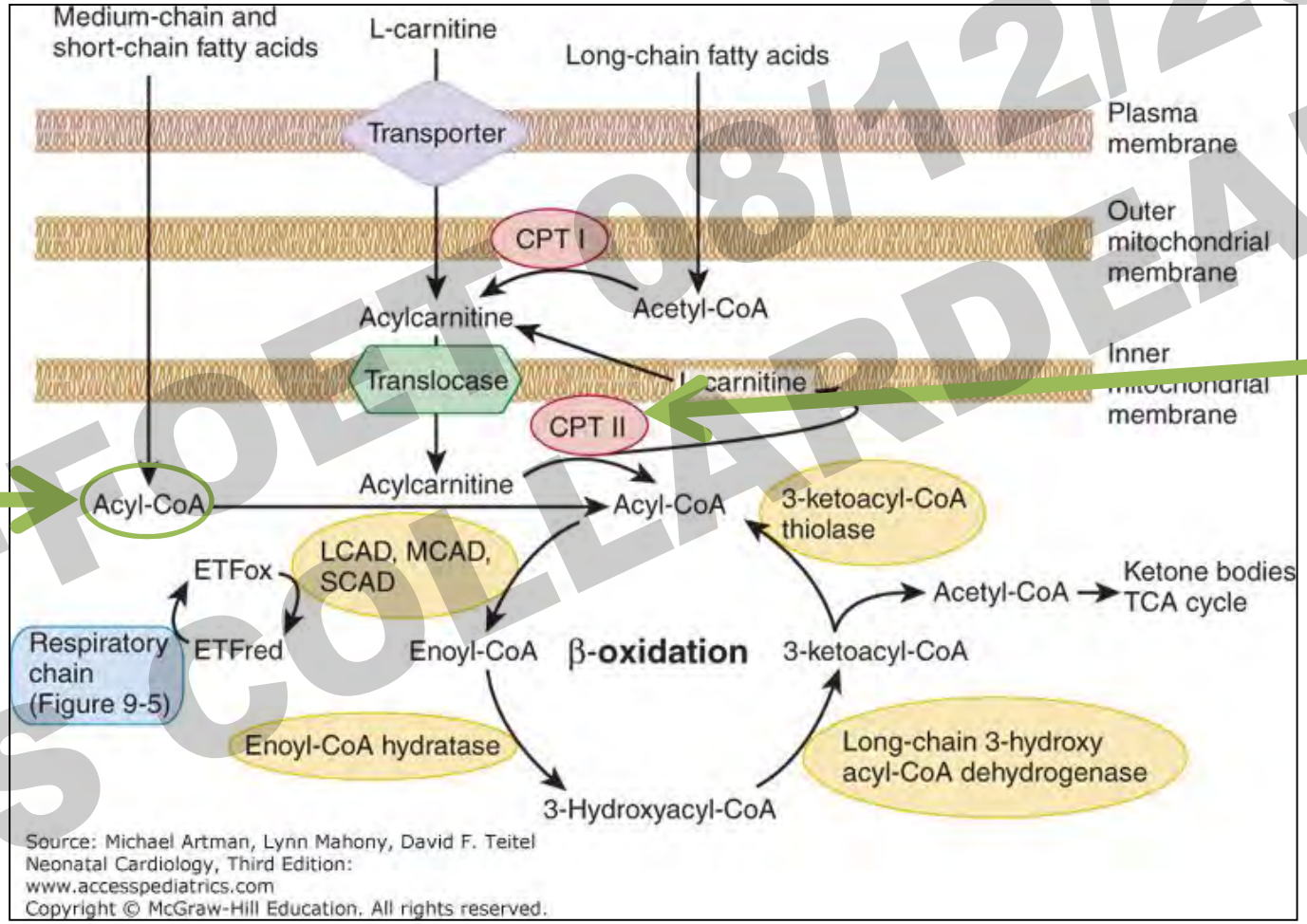
**Défaut d'énergie**




Source: Michael Artman, Lynn Mahony, David F. Teitel
Neonatal Cardiology, Third Edition:
www.accesspediatrics.com

# Gros reins hyperéchogènes avec kystes

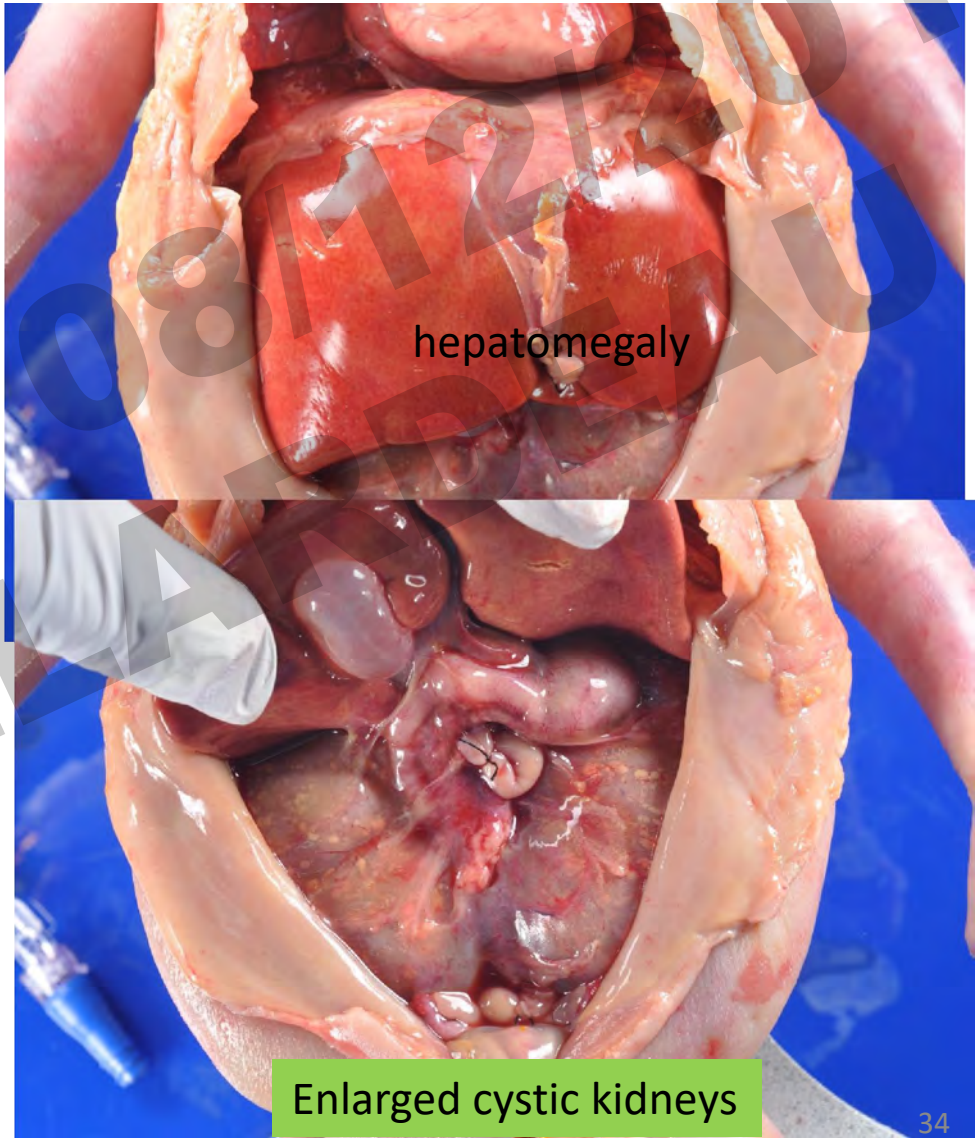
Multiple acyl-CoA dehydrogenase deficiency MADD




Carnitine Palmityl Transferase deficiency type II

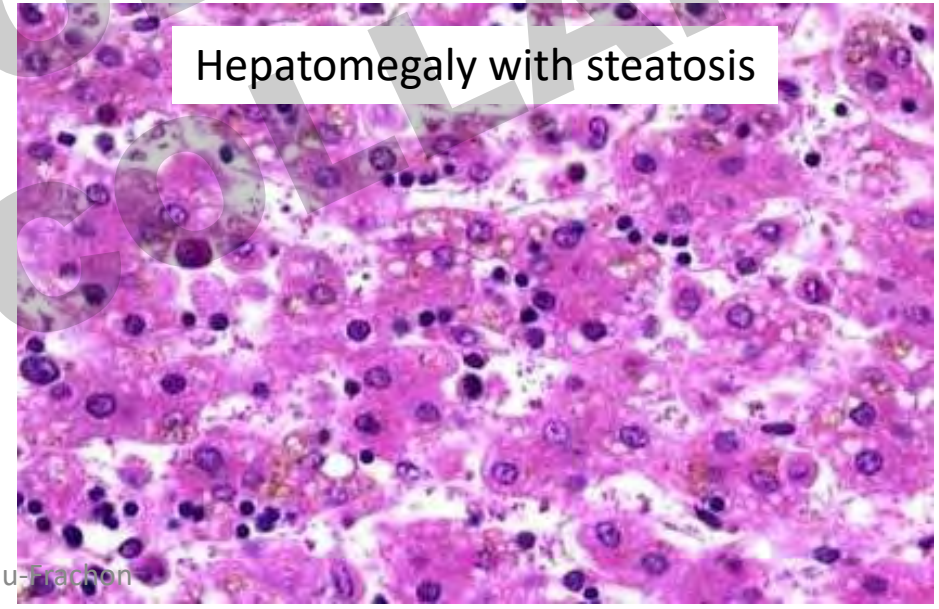
# Multiple acyl-CoA dehydrogenase deficiency MADD (Glutaric acidemia type 2)


31 GW, courtesy of E Ruchelli, CHOP



# Multiple acyl-CoA dehydrogenase deficiency MADD (Glutaric acidemia type 2)

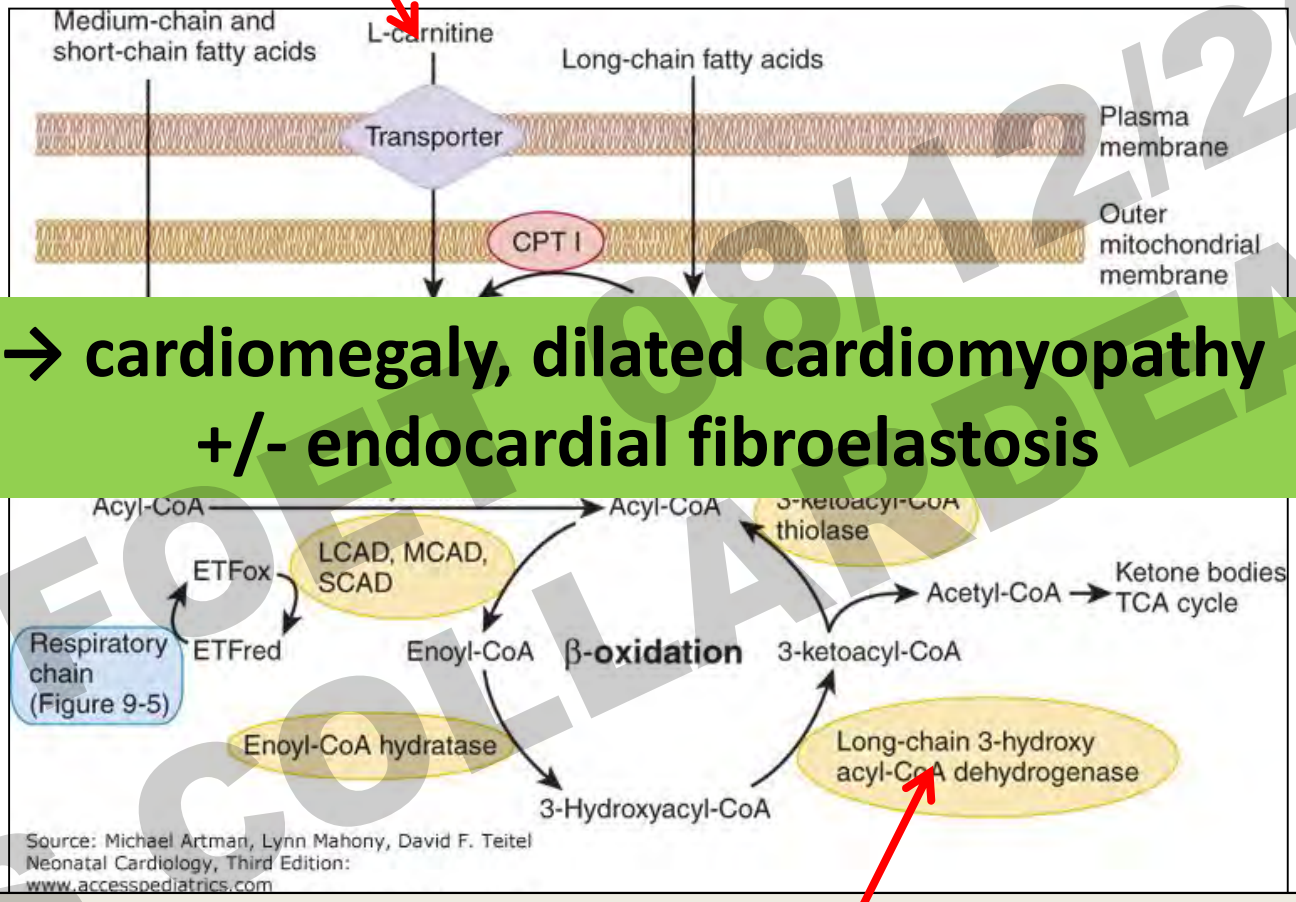
Dysplastic & cystic kidneys



Hepatomegaly with steatosis

# Hydrops + heart failure

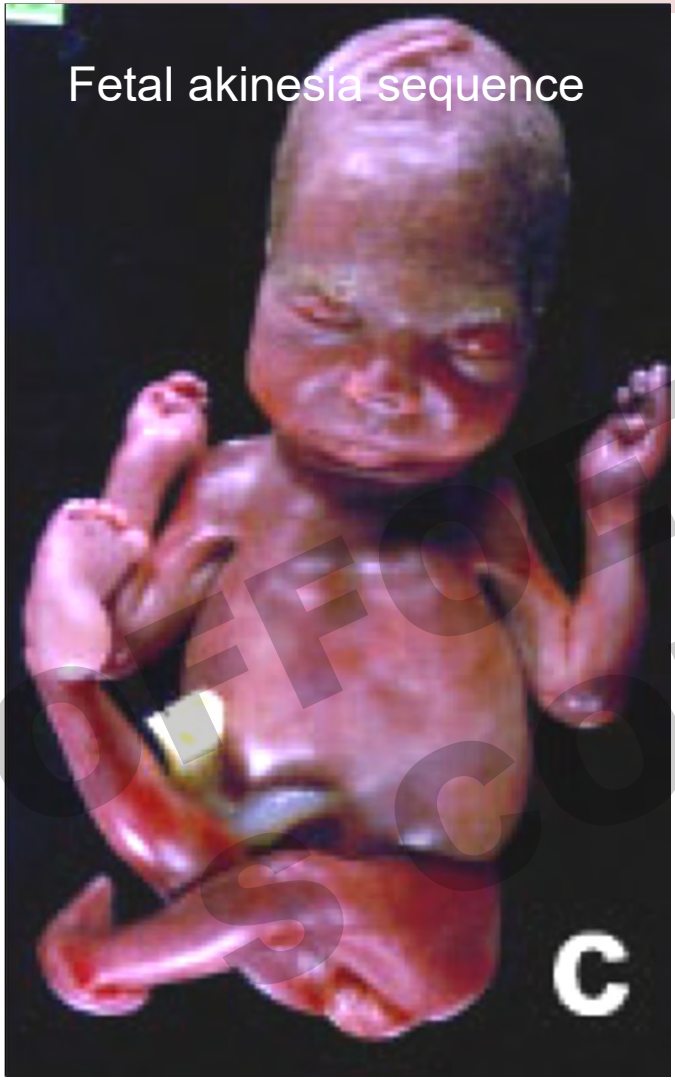
Steenhout P et al: **Carnitine deficiency with cardiomyopathy presenting as neonatal hydrops**: successful response to **carnitine therapy**. J Inherit Metab Dis 1990, 13:69–75.

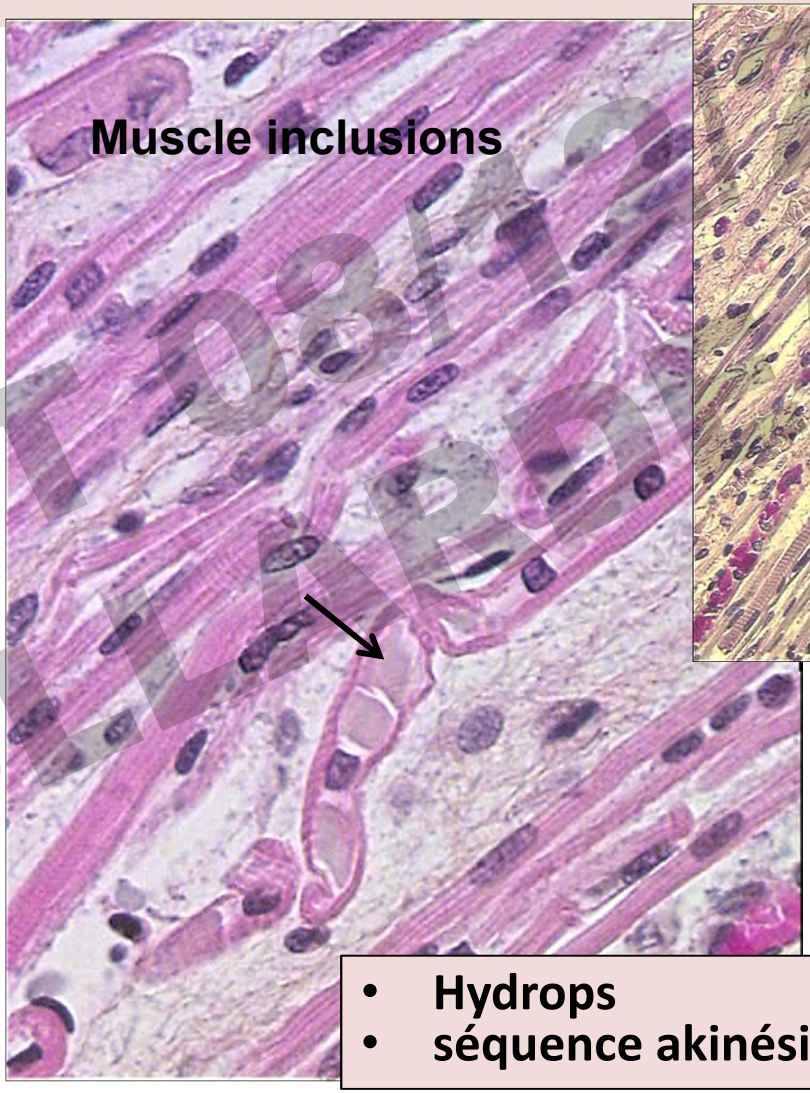


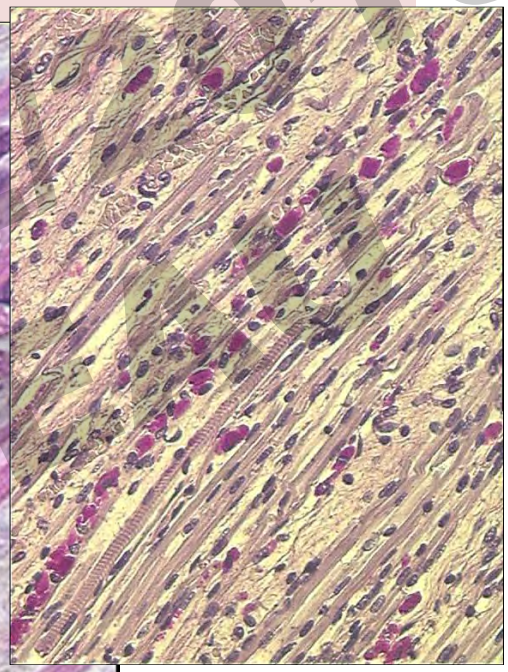

**→ cardiomegaly, dilated cardiomyopathy +/- endocardial fibroelastosis**

Tercanli S et al : Increased nuchal translucency in a case of long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency. Fetal Diagn Ther 2000, 15:322–325.: "**At 31 weeks of gestation the fetus developed a cardiomegaly and a hydrops"**

# Glycogénose de type IV



**PAS staining +**

- **Hydrops**
- **séquence akinésie fœtale**

Courtesy of Dr A Coulomb, Hop Trousseau, Paris

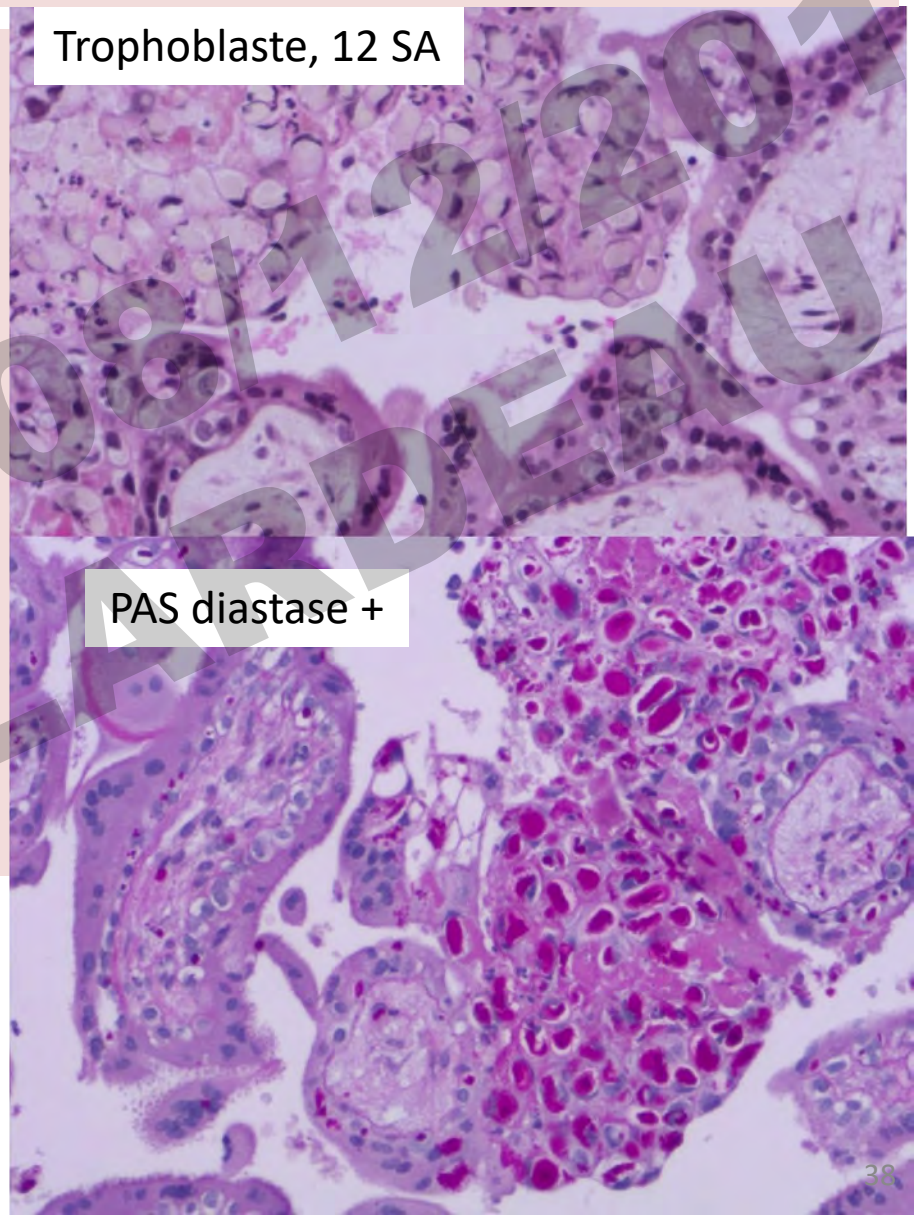
# Glycogénose de type IV

**Inclusion cytoplasmique** en verre dépoli de glycogène de structure anormale (Glycogen Branching Enzyme deficiency, GBE1) gene, AR)

- **Foie**
- **Cœur**
- **Muscle**
- **Cerveau**
- **Placenta (trophoblaste)**

**viscéromégalie**

**PAS +**
**PAS diastase /amylase +**



# Cytopathies mitochondriales

## ANTENATAL MANIFESTATIONS OF MITOCHONDRIAL RESPIRATORY CHAIN DEFICIENCY

JÜRGEN-CHRISTOPH VON KLEIST-RETZOW, MD, VALÉRIE CORMIER-DAIRE, MD, PHD, GÉRALDINE VIOT, MD, ALICE GOLDENBERG, MD, BECKY MARDACH, MD, JEANNE AMIEL, MD, PHILIPPE SAADA, MD, YVES DUMEZ, MD, PHD, FRANCIS BRUNELLE, JEAN-MARIE SAUDUBRAY, MD, DOMINIQUE CHRÉTIEN, PHD, AGNÈS RÖTIG, PHD, PIERRE RUSTIN, PHD, ARNOLD MUNNICH, MD, PHD, AND PASCALE DE LONLAY, MD, PHD

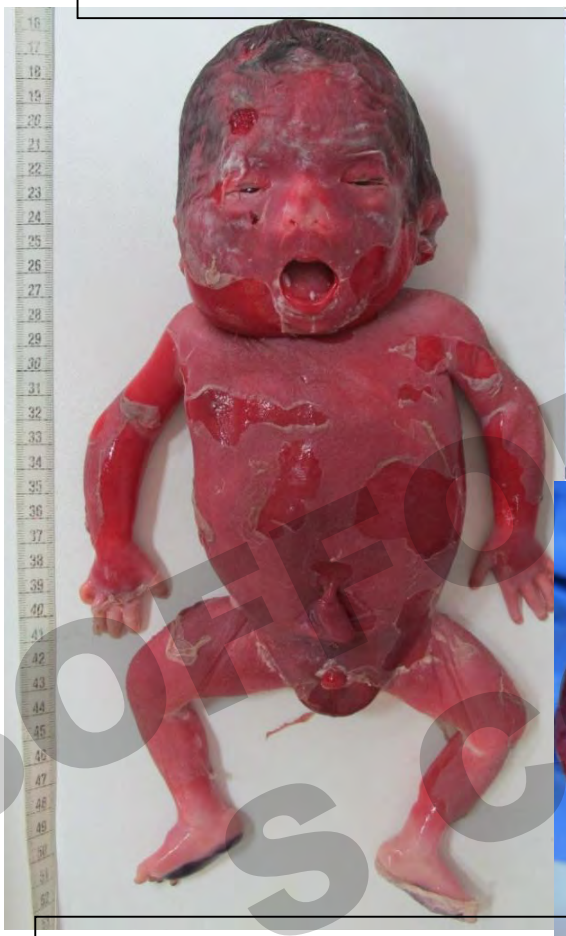
The Journal of Pediatrics • August 2003

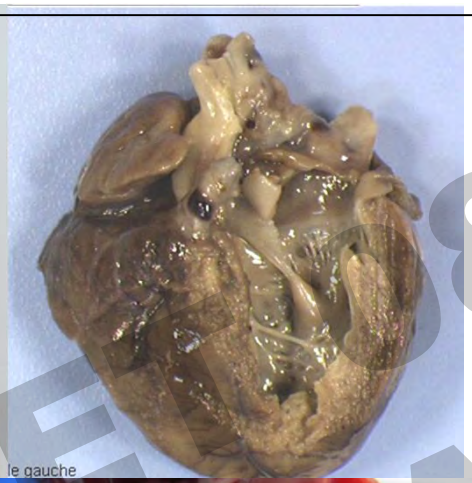
- **RCIU**
- **anasarque**
- Tableau de type **CHARGE**
- Tableau de type **VACTERL**
- Phénotype **hémochromatose néonatale**
- **Cardiomégalie, défaillance cardiaque**
- **Reins kystiques**
- Atteintes **neurologiques** : microcéphalie, hydrocéphalie, calcifications intracrâniennes, agénésie du CC, leucomalacie

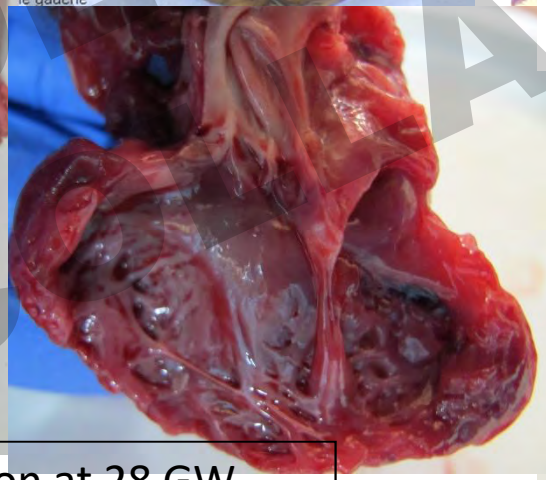
**Foie, muscle, reins, cœur, SNC:**
**Atteinte isolée ou multisystémique**

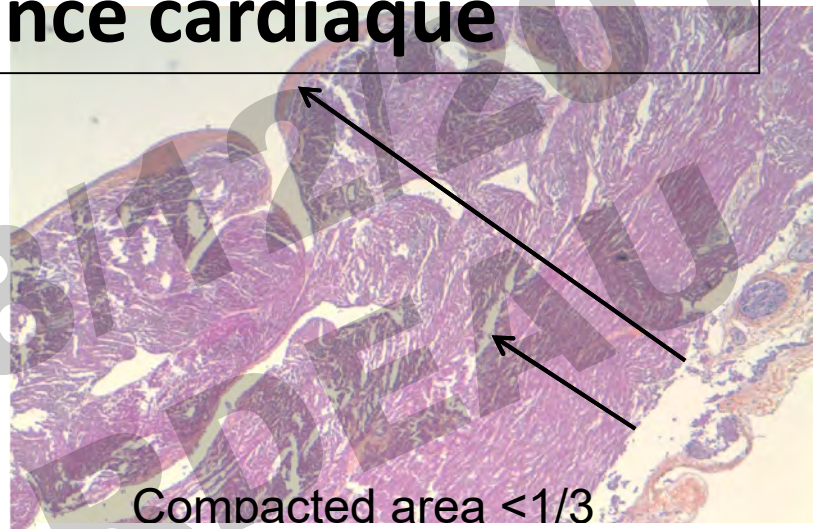
# Barth syndrome (Mitochondrial respiratory chain disorders)
# Mutation *TAZ* gene +, X-linked

## anasarque + défaillance cardiaque

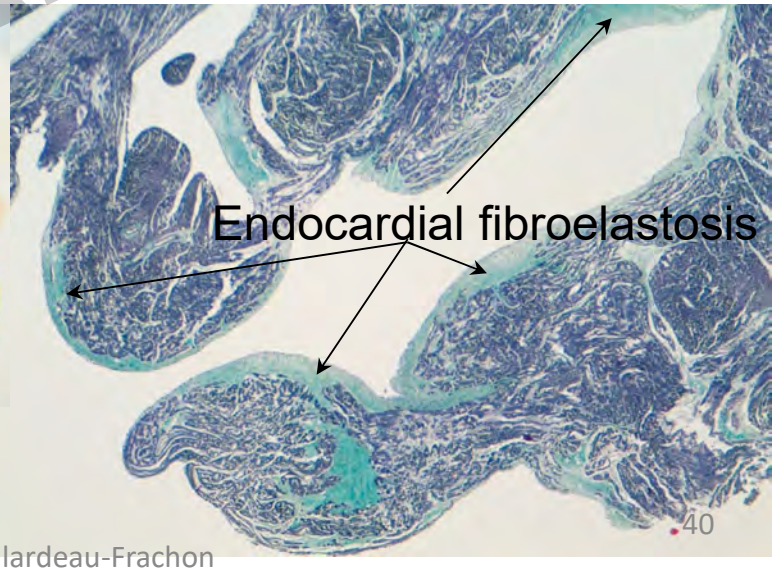









**Left ventricular non compaction**




Male foetus - Abortion at 28 GW
US: hydrops and ventricular dysfunction with pericardial effusion

# Pearson bone marrow-pancreas syndrome

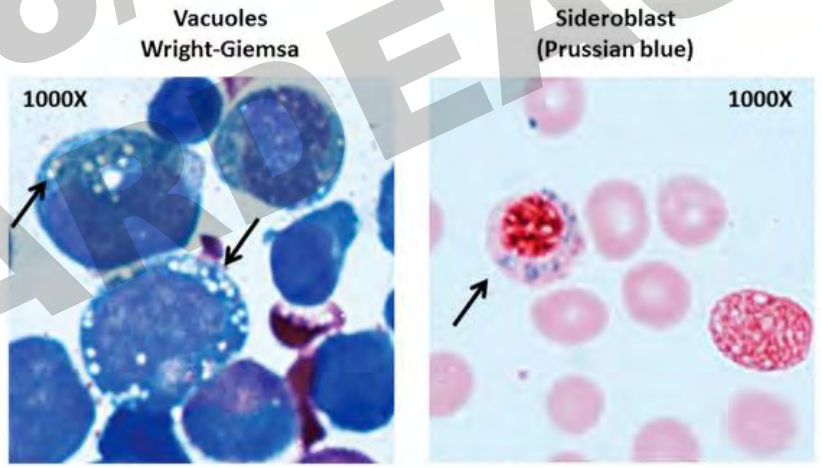
**Hydrops + défaillance cardiaque du fait de l'anémie**

Chin Med J (Engl). 2003 Dec;116(12):1952-4.

**Pearson's syndrome: a rare cause of non-immune hydrops fetalis.**

Li CH[1], Lam CW, Lee CW, Kwong NS, Szeto SC.

- Mitochondrial DNA deletion syndrome
- ↗ lactate/pyruvate ratio
- Refractory macrocytic **sideroblastic anemia (Perls +)**
- **Vacuolization of bone marrow precursors**
- Exocrine pancreatic dysfunction (pancreas fibrosis) during infancy

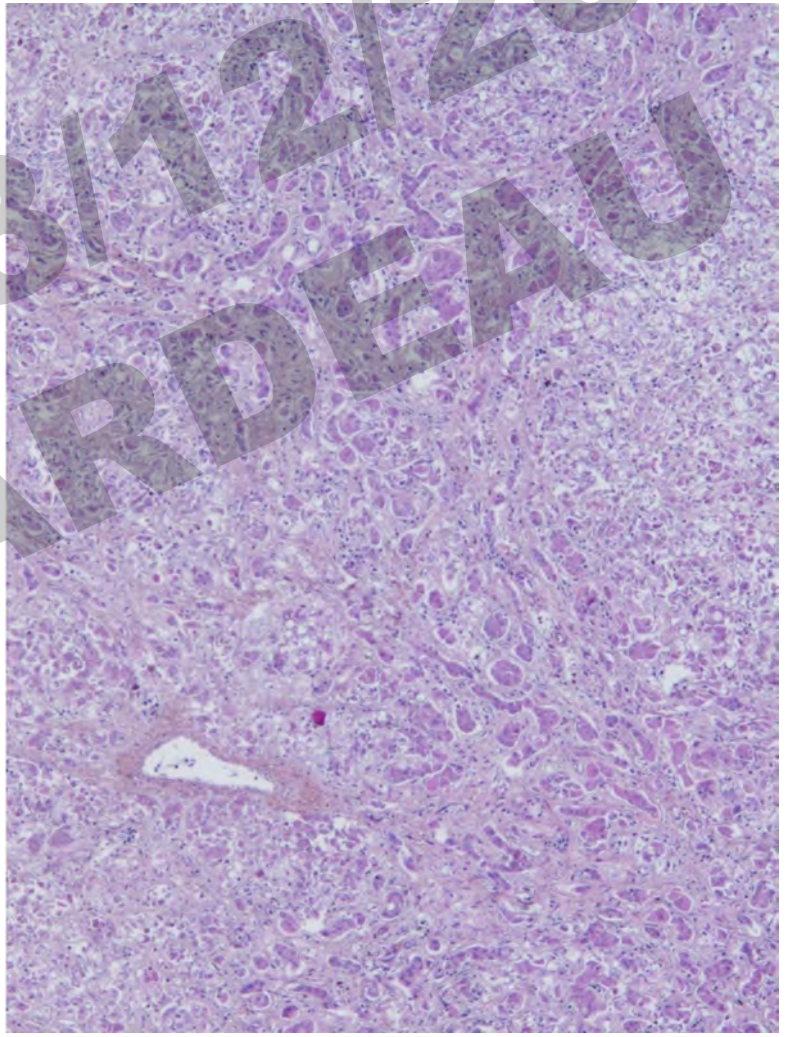



Bone marrow from a patient with PS. Left: vacuoles in myeloid precursors; right: a ringed sideroblast. See Figure 1E in the article by Gagne et al that begins on page 437.

**→ myelogram or bone marrow sample**

# Mutation de DGUOK

- Nouveau-né, à la naissance
- Sd hépato-rénal
- RCIU et Retard psychomoteur
- Difficultés alimentaire
- Hypotonie, Nystagmus
- Ictère, Hépatomégalie, Ascite
- **Déplétion de ADN mitochondrial**
- Phénotype HN
  - Stéatose focale
  - Prolifération cholangiolaire
  - Surcharge en fer mixte



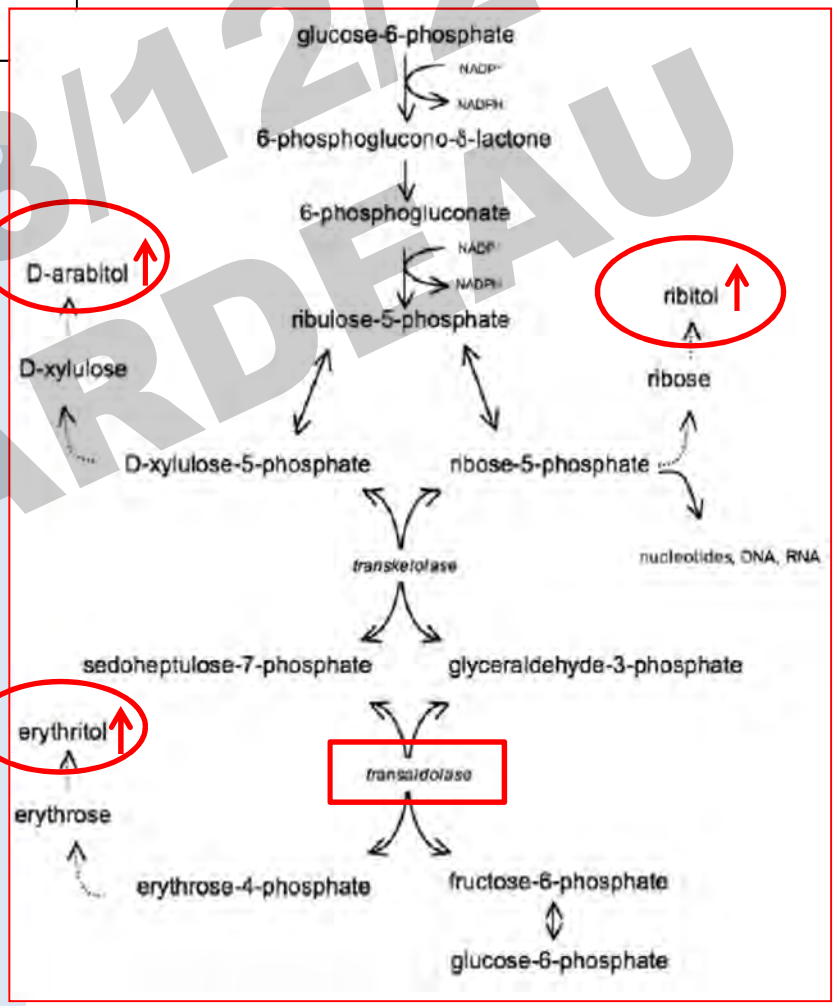
# Déficit en transaldolase

TRANSALDOLASE DEFICIENCY: A NEW CAUSE OF HYDROPS FETALIS AND NEONATAL MULTI-ORGAN DISEASE

VASSILI VALAYANNOPOULOS, MD, NANDA M. VERHOEVEN, PHD, KARINE MENTION, MD, GAJJA S. SALOMONS, PHD, DANIÈLE SOMMELET, MD, PHD, MARIE GONZALES, MD, GUY TOUATI, MD, PASCALE DE LONLAY, MD, PHD, CORNELIS JAKOBS, PHD, AND JEAN-MARIE SAUDUBRAY, MD, PHD

The Journal of Pediatrics • November 2006

- Transaldolase : a key enzyme in the **pentose phosphate pathway**
- Same pathway implied in G6PD deficiency
- important source of NADPH
- Ribose 5 phosphate =building block of DNA and RNA
- **Accumulation of polyols (urine):** ribitol, D-arabitol and erythritol
- **Autosomal recessive: TALDO1 gene**



# Déficit en transaldolase


**Wrinkly skin**


**Extensive cutis laxa phenotype**

Pictures from

J Inherit Metab Dis
DOI 10.1007/s10545-012-9577-8

ORIGINAL ARTICLE

**Transaldolase deficiency: report of 12 new cases and further delineation of the phenotype**

Wafaa Eyaid · Talal Al Harbi · Shamsa Anazi · Mirjam M. C. Wamelink · Cornelis Jakobs · Mohammad Al Salammah · Mohammed Al Balwi · Majid Alfadhel · Fowzan S. Alkuraya

- **IUGR**
- Hirsutism, low hair line, cutis laxa,
- Brachycephaly, dolichocephaly
- Antimongoloid slants, low-set ears, exophthalmia, and broad nasal bridge
- **Hepatosplenomegaly**
- Congenital heart disease

# Déficit en transaldolase

JIMD Reports
DOI 10.1007/8904_2015_474

CASE REPORT

**Transaldolase Deficiency: A New Case Expands the Phenotypic Spectrum**

Ehud Banne · Vardiella Meiner · Avraham Shaag · Rachel Katz-Brull · Ayelet Gamliel · Stanley Korman · Smadar Horowitz Cederboim · Morasha Plesser Duvdevani · Ayala Frumkin · Amir Zilkha · Vadim Kapuller · Dan Arbell · Elite Cohen · Smadar Eventov-Friedman

IUGR & echogenic bowels

**Liver anomalies:**

- Neonatal haemochromatosis phenotype
- Steatosis
- Portal Fibrosis

Table 1 Clinical features of previously described patients with TALDO deficiency and comparison to the present patient

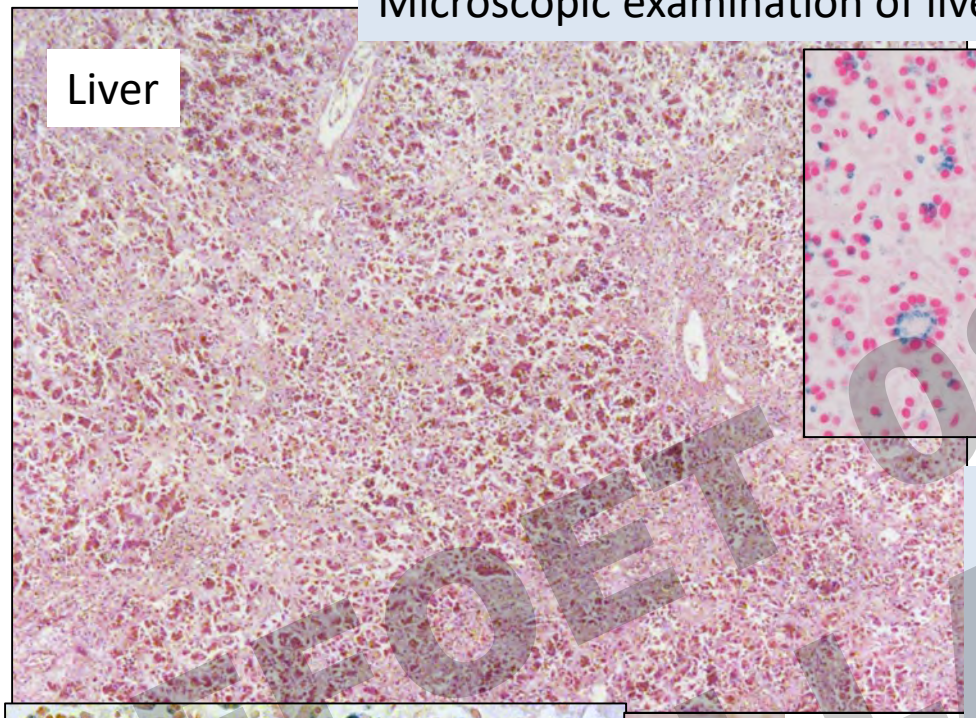
| Feature | Reported cases (percent of cases) | Present patient |
|---|---|---|
| Consanguinity | 25/31 (80.6) | + |
| Dysmorphism | 18/31 (58) | + |
| Liver dysfunction | 26/31 (83.8) | + |
| Hepatosplenomegaly | 30/31 (96) | +/− (only splenomegaly) |
| Anemia | 27/31 (87) | − |
| Thrombocytopenia | 27/31 (87) | + |
| Cardiac | 23/31 (74) | + |
| Neonatal edema | 8/31 (25.8) | − |
| Renal | 11/31 (35.5) | + |
| Respiratory | 5/31 (16) | − |
| Developmental delay | 2/31 (6) | NA |
| Additional features found | Hypertrichosis<br>Hypotonia | Hypothyroidism<br>Hyperechogenic bowel<br>Hypertrichosis<br>Neonatal hypotonia |

Data collected from previous reports (Leduc et al. 2014; Verhoeven et al. 2001; Verhoeven et al. 2005; Valayannopoulos et al. 2006; Wamelink et al. 2008a; Al-Shamsi et al. 2015; Tylki-Szymanska et al. 2009; Tylki-Szymanska et al. 2014; Eyaid et al. 2013; Balasubramaniam et al. 2011)

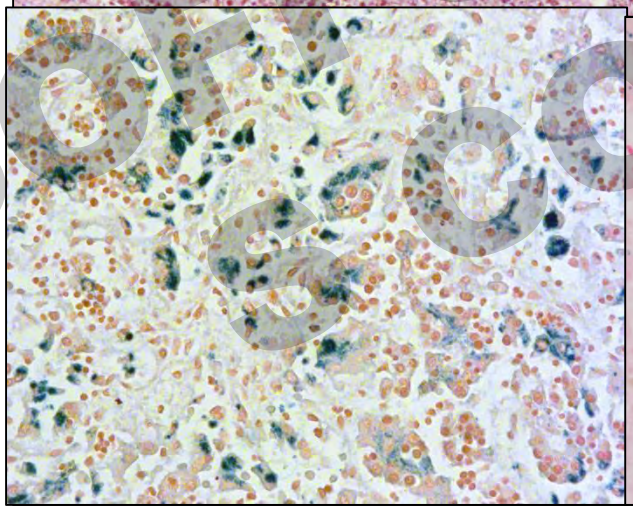
hydrops

TRANSALDOLASE DEFICIENCY: A NEW CAUSE OF HYDROPS FETALIS AND NEONATAL MULTI-ORGAN DISEASE

Microscopic examination of liver & organs from this case





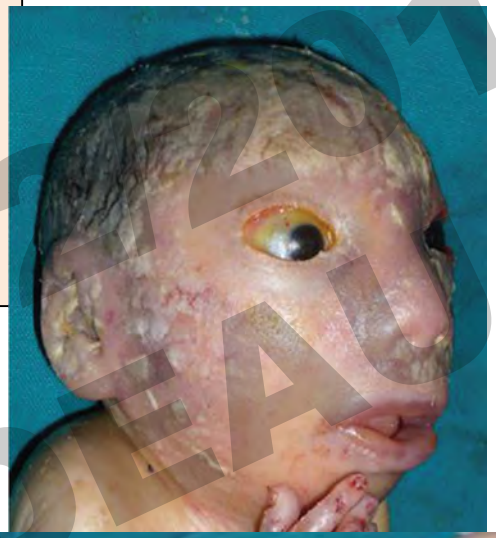



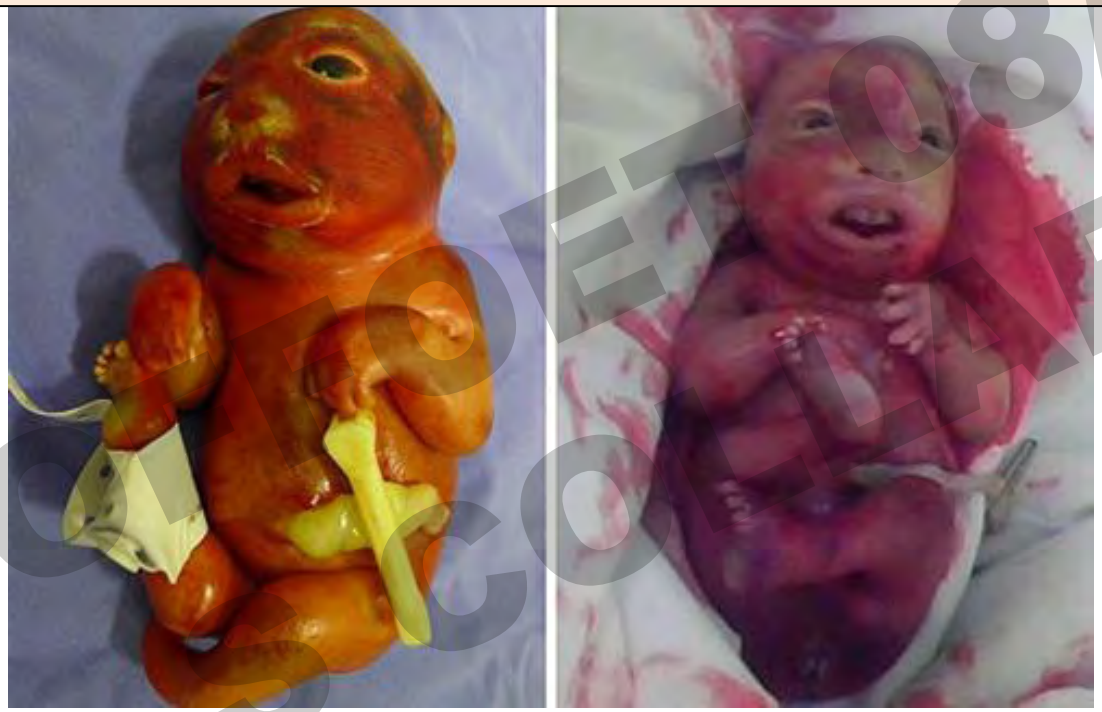

**NH PHENOTYPE AND IEM**

- Transaldolase deficiency
- Mitochondrial respiratory chain disorders
  - DGUOK mutations
  - GRACILE syndrome
  - PEARSON syndrome
- Zellweger syndrome
- PMM2-CDG

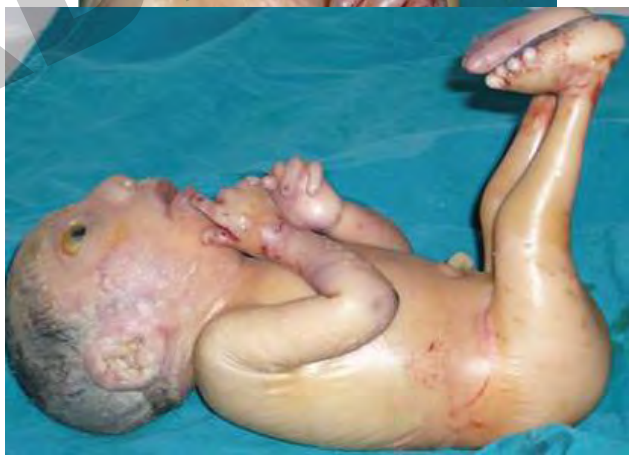
# Aminoacidopathie: Neu-Laxova syndrome

- **Anomalies de synthèse de la sérine**
- gènes: *PHGDH*, *PSAT1* and *PSPH,*
- *autosomique récessif*
- **RCIU, microcéphalie, ichtyose, akinésie**





From Mattos EP, et al, Am J Med Genet A. 2015 Jun;167(6):1323-9.

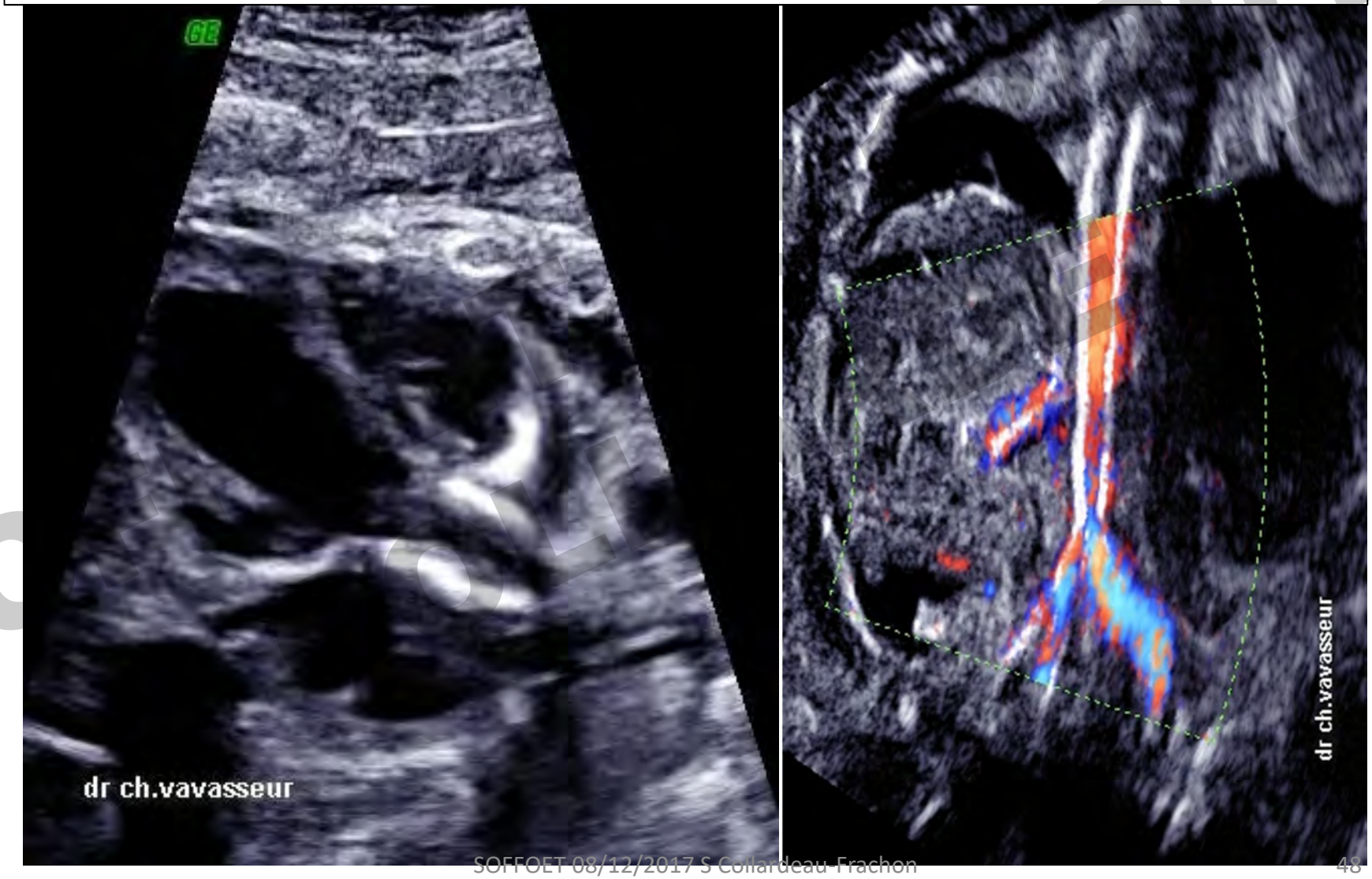


*From Tarim E, Bolat F. J Turk Ger Gynecol Assoc. 2010 Dec 1;11(4):225-7.*

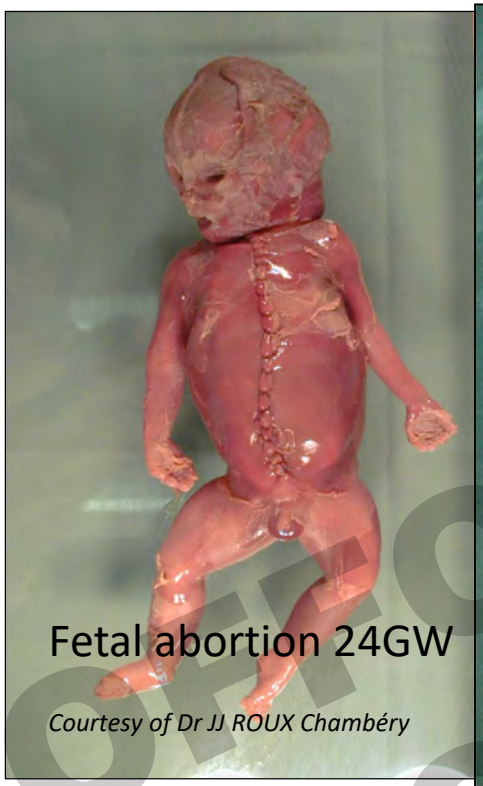
*Darouich S, Boujelbene N, Kehila M, Chanoufi MB, Reziga H, Gaigi S, Masmoudi A. [Neu-Laxova syndrome: Three case reports and a review of the literature]. Ann Pathol. 2016 Aug;36(4):235-44.*

# Generalized arterial calcifications of infancy (GACI), AR

Hydrops + calcifications

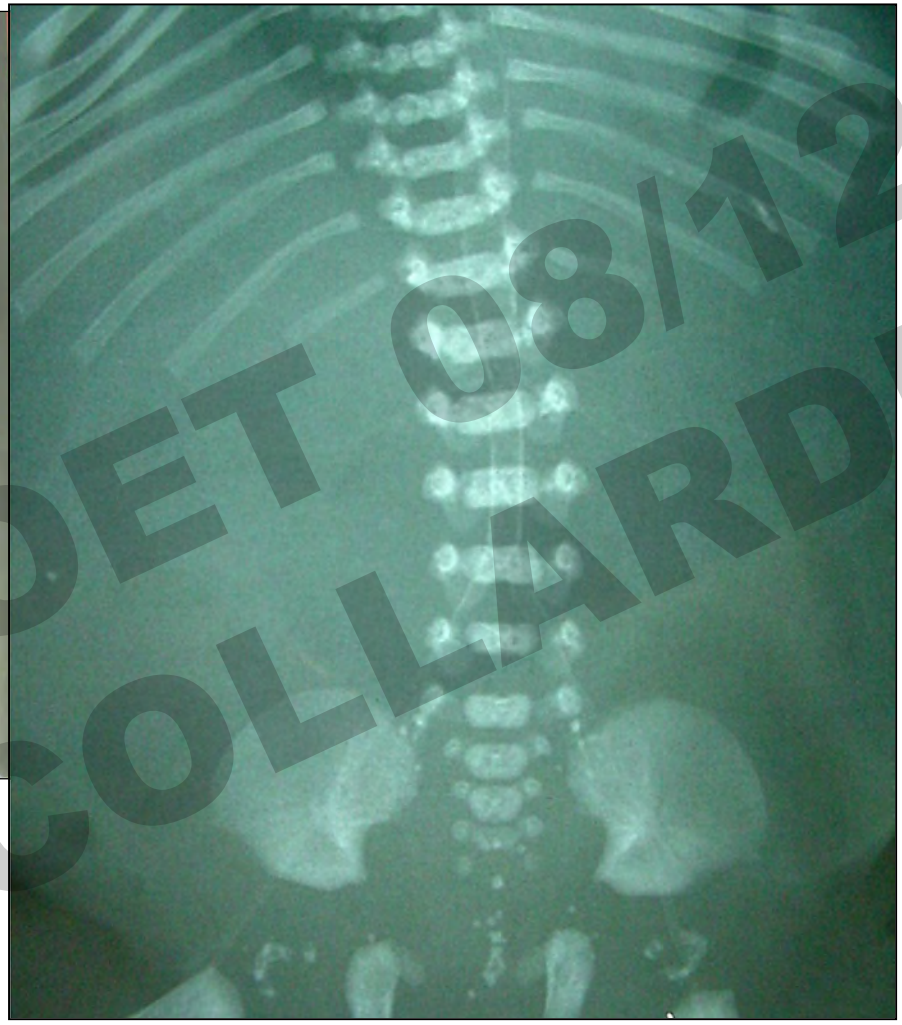


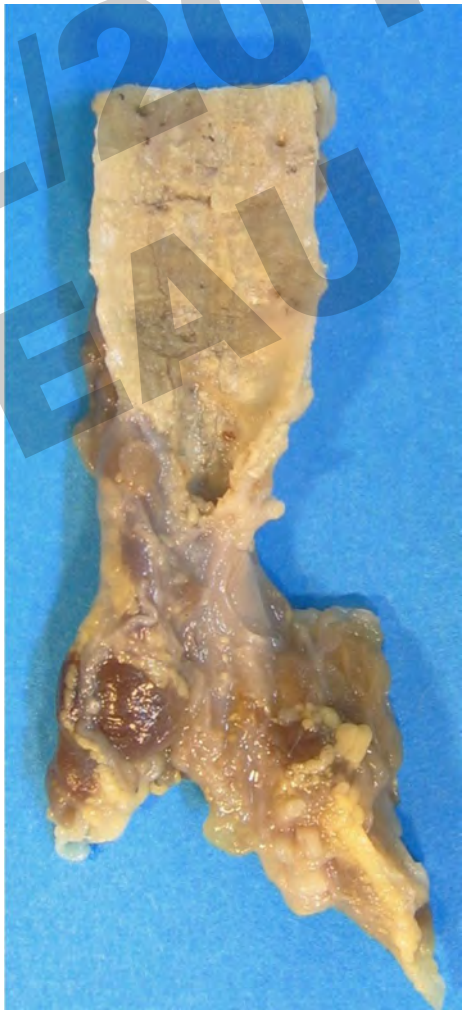
# Generalized arterial calcifications of infancy (GACI)



Fetal abortion 24GW

*Courtesy of Dr JJ ROUX Chambéry*





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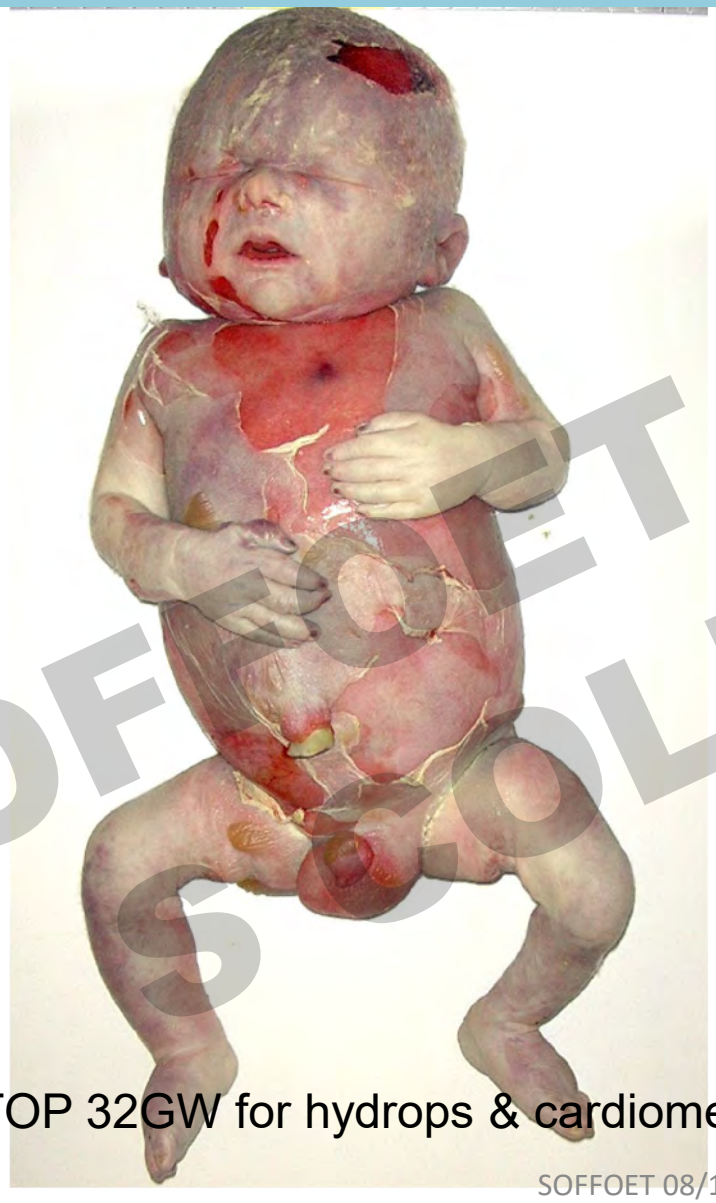
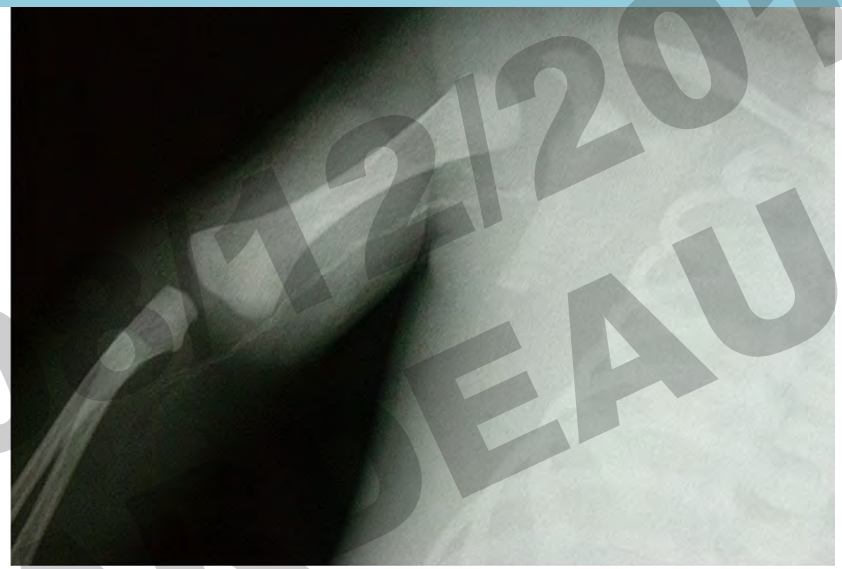
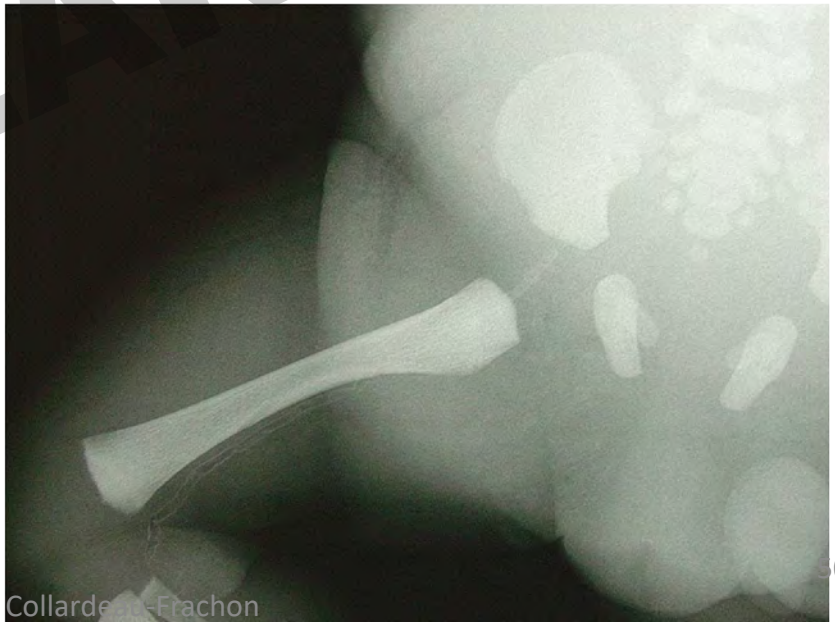
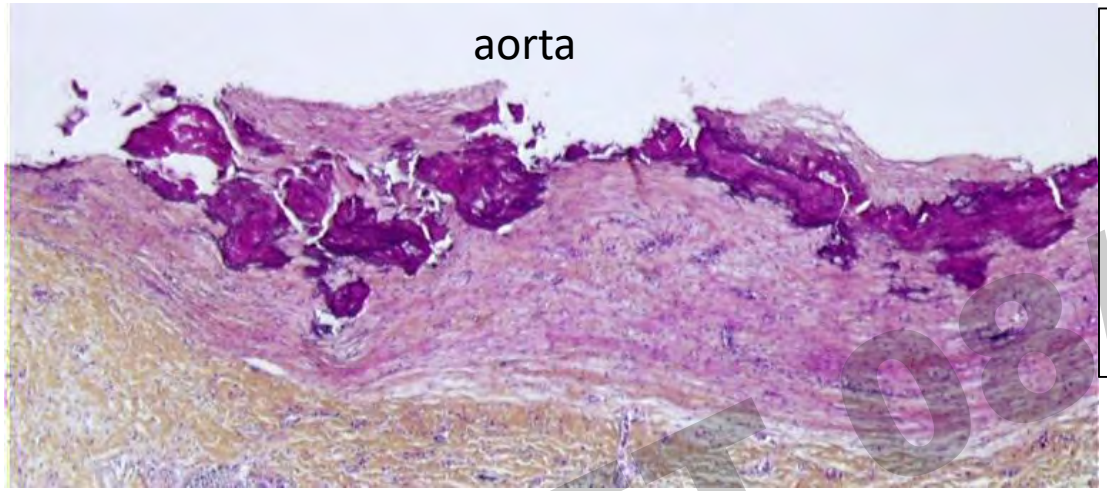


TOP 32GW for hydrops & cardiomegaly



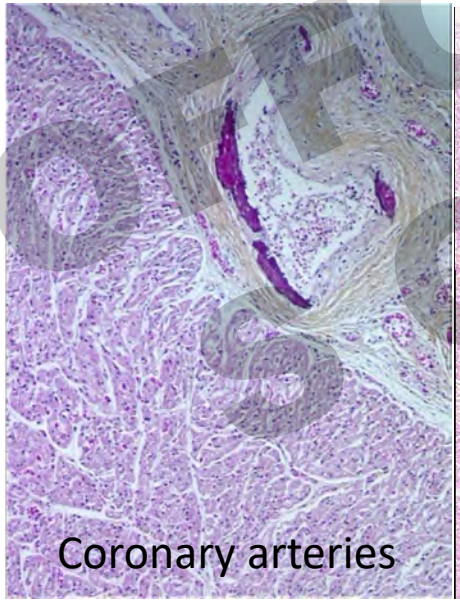


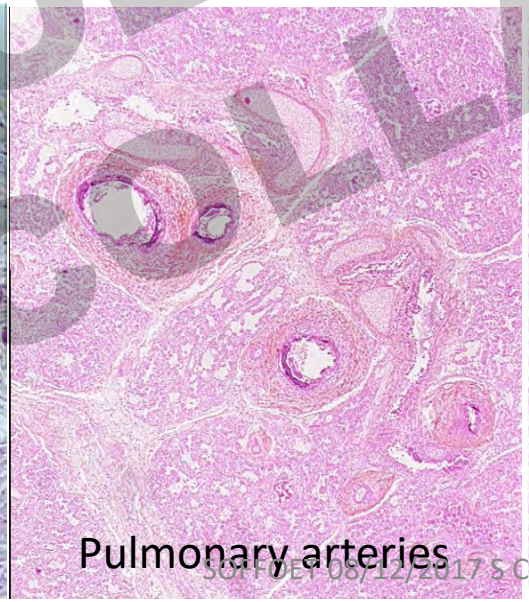
# Generalized arterial calcifications of infancy (GACI), AR

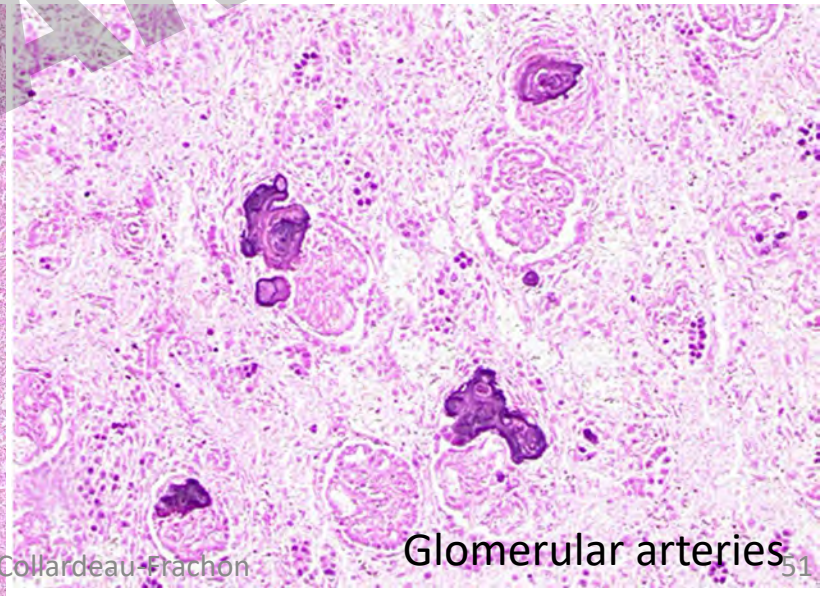



*Nitschke Y, Baujat G, Botschen U et al (2012) Generalized arterial calcification of infancy and pseudoxanthoma elasticum can be caused by **mutations in either ENPP1 or ABCC6**. AmJ HumGenet 90:25–39*

myocardial ischemia → heart failure → HF


Coronary arteries


Pulmonary arteries


Glomerular arteries

PRENATAL DIAGNOSIS
*Prenat Diagn* 2003; **23**: 25–30.
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/pd.491

SHORT COMMUNICATION

**Congenital erythropoietic porphyria (Günther's disease): two cases with very early prenatal manifestation and cystic hygroma**

E. Pannier[1]*, G. Viot[1], M. C. Aubry[1], G. Grange[1], J. Tantau[2], C. Fallet-Blanco[3], F. Muller[4] and D. Cabrol[1]

# Hydrops + défaillance cardiaque


- Severe IUGR
- **Anemia**
- **Dark-brown coloration of AF, blood and viscera**
- +/- Hyperechogenic kidneys and bones

Autosomal recessive disease. **Heme biosynthetic pathway defect**: uroporphyrinogen III synthase (UROIIIS) enzyme deficiency→ **accumulation of URO I in erythrocytes** leads to **hemolysis**. URO I deposits in tissues and bones and is excreted in the urine and feces. Sunlight and other forms of ultraviolet light activates the photocatalytic URO I resulting in tissue blistering (severe cutaneous photosensitivity, bullous lesions on sun-exposed zones….)

# Conclusion

- Nombreuses MHM à révélation anténatale avec plusieurs tableaux
  - voir tableaux synthétiques en fin de diaporama
- Anasarque un signe majeur mais pas le seul
- Hétérogénéité intrafamiliale: tableaux +/- complets

# Anasarque/ hydrops: quelle MHM?

## Lysosomal storage diseases (LSD) +++

ORPHANET JOURNAL OF RARE DISEASES

RESEARCH Open Access

Lysosomal storage disorder in non-immunological hydrops fetalis (NIHF) - more common than assumed? Report of four cases with transient NIHF and a review of the literature

Catharina Whybra[*], Eugen Mengel[1], Alexandra Russo[2], Franz Bahlmann[3], Christoph Kampmann[3], Michael Beck[2], Ute Fuchs[4] and Eva Wildenberger[1]

**Non lysosomal IEM**

**Glycogenosis:**

Type IV (Anderson disease): [31,32]

**Congenital disorder of glycosylation:**

CDG Ia [42,43]

**Peroxismal disorder:**

Zellweger syndrome [44]

**Fatty acid oxidation defects:**

Long-chain-hydroxyacyl CoA dehydrogenase deficiency (LCHAD) [50]

Primary carnitine deficiency [52]

**Cholesterol biosynthesis defects:**

Smith-Lemli-Opitz Syndrome [57]

Greenberg syndrome: Hydrops-ectopic calcification moth-eaten skeletal dysplasia [59]

Conradi Huenermann: Chondrodysplasia punctata [61] (X linked disorder: male fetus)

**Others:**

Citric-acid cycle defect (Fumarase deficiency) [64,65]

Neonatal hemochromatosis [20]

Transaldolase deficiency [68]

S-adenosylhomocysteine hydrolase deficiency [69]

Congenital erythropoietic porphyria [70]

Whybra *et al. Orphanet Journal of Rare Diseases* 2012, **7**:86

# Anasarque/ hydrops: quelle MHM?

## Lysosomal storage diseases (LSD) +++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Ty

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**Peroxismal disorder:**

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F

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d

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Dursun A et al : **Zellweger syndrome with unusual findings: non-immune hydrops fetalis**, dermal erythropoiesis and hypoplastic toe nails. J Inherit Metab Dis 2009.

Maymon R, Ogle RF, Chitty LS. **Smith-Lemli-Opitz syndrome** presenting with persisting nuchal oedema and **non-immune hydrops**. Prenat Diagn. 1999 Feb;19(2):105-7.

Whybra *et al. Orphanet Journal of Rare Diseases* 2012, 7:86

# Anasarque/ hydrops: quelle MHM?

## Non lysosomal IEM

**Glycogenosis:**

Type IV (Anderson disease): [31,32]

**Congenital disorder of glycosylation:**

CDG Ia [42,43]

And other N-CDG

**Peroxismal disorder:**

Zellweger syndrome [44]

**Fatty acid oxidation defects:**

Long-chain-hydroxyacyl CoA dehydrogenase deficiency (LCHAD) [50]

Primary carnitine deficiency [52]

And MADD (glutaric aciduria type II)

**Mitochondrial respiratory chain disorders**

Barth syndrome

Pearson syndrome

DGUOK

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phenotype

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Congenital erythropoietic porphyria [70]

**Generalized arterial calcifications of infancy (GACI)**

# Conclusion

- **Importance d'une autopsie complète** pour orienter le diagnostic **ET** les études biochimiques complémentaires
  - Radiographies du squelette indispensables
  - Examen macroscopique minutieux
  - Examen microscopique de tous les organes foetaux
- **Examen du placenta**:
  - diagnostic des maladies lysosomales et GSD IV
  - de façon très précoce
  - possible en extemporané sur biopsie de trophoblates
  - utile si refus d'autopsie ou FCS précoce

# Conclusion

**Prélèvements pour investigations**

**biochimiques et de biologie moléculaire**

- **Ponction des épanchements**: ascite ou liquide pleural surtout s'il n'y a pas eu de PLA : 15 ml
  - détection des métabolites accumulés dans le surnageant après centrifugation et culture cellulaire du culot
- **Tissus frais pour culture cellulaire:** peau, poumon, rein, muscle
  - Whole-cell techniques
  - Mesure des activités enzymatiques
  - Extraction ADN pour identifier les mutations
- **Tissus congelés**: foie, rein, cerveau, thymus, placenta….
  - Mesure des activités enzymatiques
  - Extraction ADN pour identifier les mutations
- ME: foie, rein, muscle….(mais non indispensable)

# Diapos synthétiques

**Hydrops + anomalies du squelette**

- Greenberg
- CPDX2
- Lysosomes: MPS VII, IV, MLII, ac sialique

**Hydrops + calcifications**

Maladies de Wolman (LSD)

GACI

**Hydrops + akinésie fœtale**

- Gaucher
- GSD IV

**Hydrops + défaillance cardiaque**

- Barth syndrome
- LCHAD deficiency
- Primary carnitine deficiency
- Pearson syndrome
- Congenital erythropoietic porphyria
- GACI

**Akinésie fœtale**

- Gaucher
- GSD4
- Neu-Laxova
- Cytopathie mt

**Reins hyperéchogènes/ kystiques**

- Zellweger
- MADD
- CPT 2
- N-CDG

**RCIU**

- Smith-Lemli Optiz syndrome
- Latho et desmostérolose
- Neu laxova
- Transaldolase deficiency
- N-CDG
- Cytopathies mitochondriales

**Anomalies des OGE**

- Smith-Lemli-Opitz (mâle)
- desmostérolose
- Antley-Bixler syndrome (POR gene)
- Déficit en transaldolase
- Cytopathie mitochondriale
- Déficit en PDH

# Anomalies du squelette

**Variable dysostosis** (LSD)

- Mucolipidosis type II
- sialic acid metabolism
- GM1 gangliosidosis
- Mucopolysaccharidoses

**Hypomineralization +/- fractures**

- Hypophosphatasie
- Akinésie foetale

**Asymétrie/ anomalies réductionnelles**

- CHILD

**Épiphyses ponctuées**

- Greenberg
- CPDX2
- Peroxisomal disorders
- LSD: mucolipidosis type II, sialic acid metabolism
- Arylsulfatase E deficiency

**Anomalies des extrémités**

- SLO
- Lathostérolose
- Antley Bixler
- ARSE
- N-CDG

# Anomalies cutanées

**Ichtyose**

- Gaucher
- CPDX2
- Neu-Laxova
- CHILD (naevus)

**Peau frippée/ridée**
**Hirsutisme**

- Déficit en transaldolase

**Odeur de pieds en sueur**

- MADD

**Anomalies de la répartition des graisses**
**Mamelons inversés**

- N-CDG

**Défaut de fermeture du tube neural:**

- O-glycosylation
- Lathostérolose
- CHILD

# Anomalies hépatiques

## Phénotype HN

- Transaldolase deficiency
- CDGs
- Zellweger
- DGUOK
- Pearson
- GRACILE

## Hépatomégalie

- Lysosome
- B oxydation des AG (MADD, CPT2)
- Cytop mit
- Transaldolase
- N-CDG

## Stéatose

- B oxydation des AG
- Cytop mit

## Anomalies de la plaque ductale

- Zellweger (ductopénie)
- N-CDG (prolifération cholangiolaire)
- Cytop mit(prolifération cholangiolaire)

# Dysmorphie faciale

## Microcéphalie

- SLO
- Lathostérolose
- Desmostérolose
- Neu Laxova
- Fumarase deficiency
- Hyperphénylalaninémie maternelle
- Cytopathie mitochondriale
- PDH
- N-CDG

## Hypoplasie étage moyen

- Lysosomes (MPSVII et IV, ML II, ac sialique)
- N-CDG
- ARSE
- CPDX2
- RCDP
- Greenberg
- Antley Bixler

## Macrocéphalie

- Acidurie glutarique de type I
- Desmostérolose
- Cytopathie mitochondriale
- MADD
- CPT2