A little more than just IUGR

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Brief discussion during prenatal round

- Young parents in good health
- G1P0
- Origin: **Afghanistan,** since 2015 in Belgium
- **Consanguinity: yes**, cousins
- NIPT normal XY, serology nl, no diabetes/HTA/thyroid problems
- Prenatal ultrasounds:
  - ➢ T1 nl
  - ➢ T2 morphology nl
  - ➢ **T3 (32w) IUGR stade 0 → (35w) stade 1; morphology nl (weight estimated at 1825g)**

'Just IUGR'

↓

Induction at 37w GA

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Delivery

- 37+1w GA
- Vaginal delivery, head position, clear amniotic fluid
- Apgar 2-5-7
- Needs **2x 5 insufflations, 2 min of ventilations, on CPAP PEEP 6, FiO2 30%**
- pH 7,22 – BE -12 – lact 5,7 – glyc 75

➔Recovers clinically quickly

➔But …

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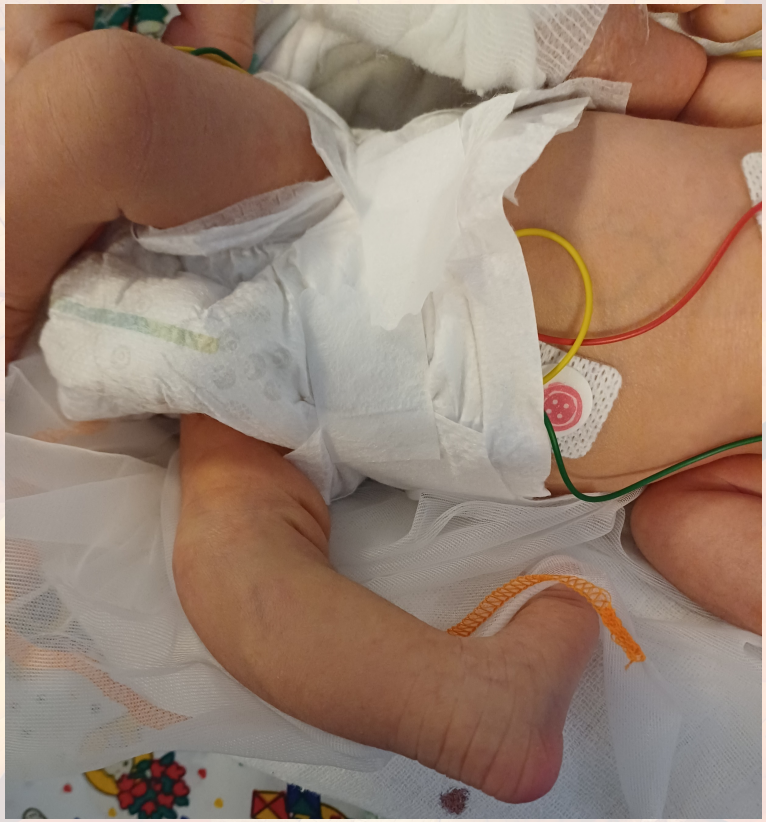

Genu recurvatum

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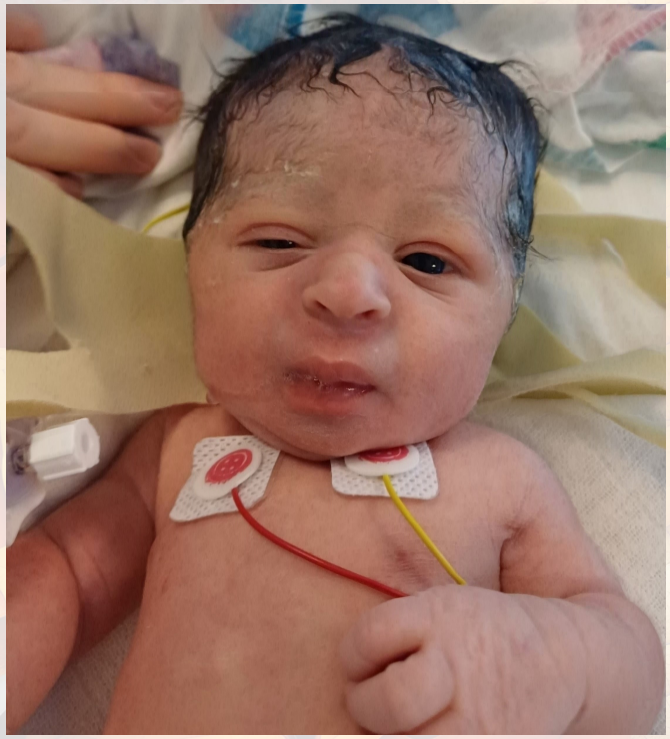

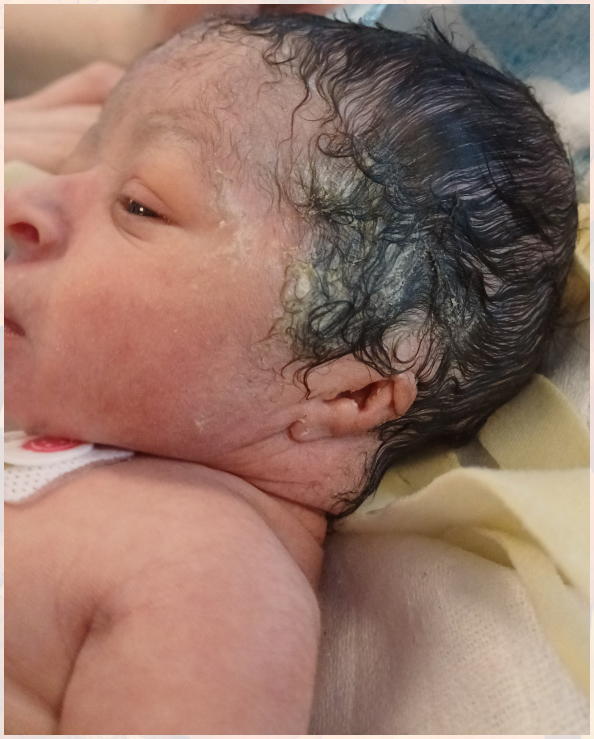

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- Normal cardio-pulmonary auscultation
- Abdomen normal
- Tonus normal, reflexes normal
- No clear hyperlaxity of other joints
- **Bilateral cryptorchidism**

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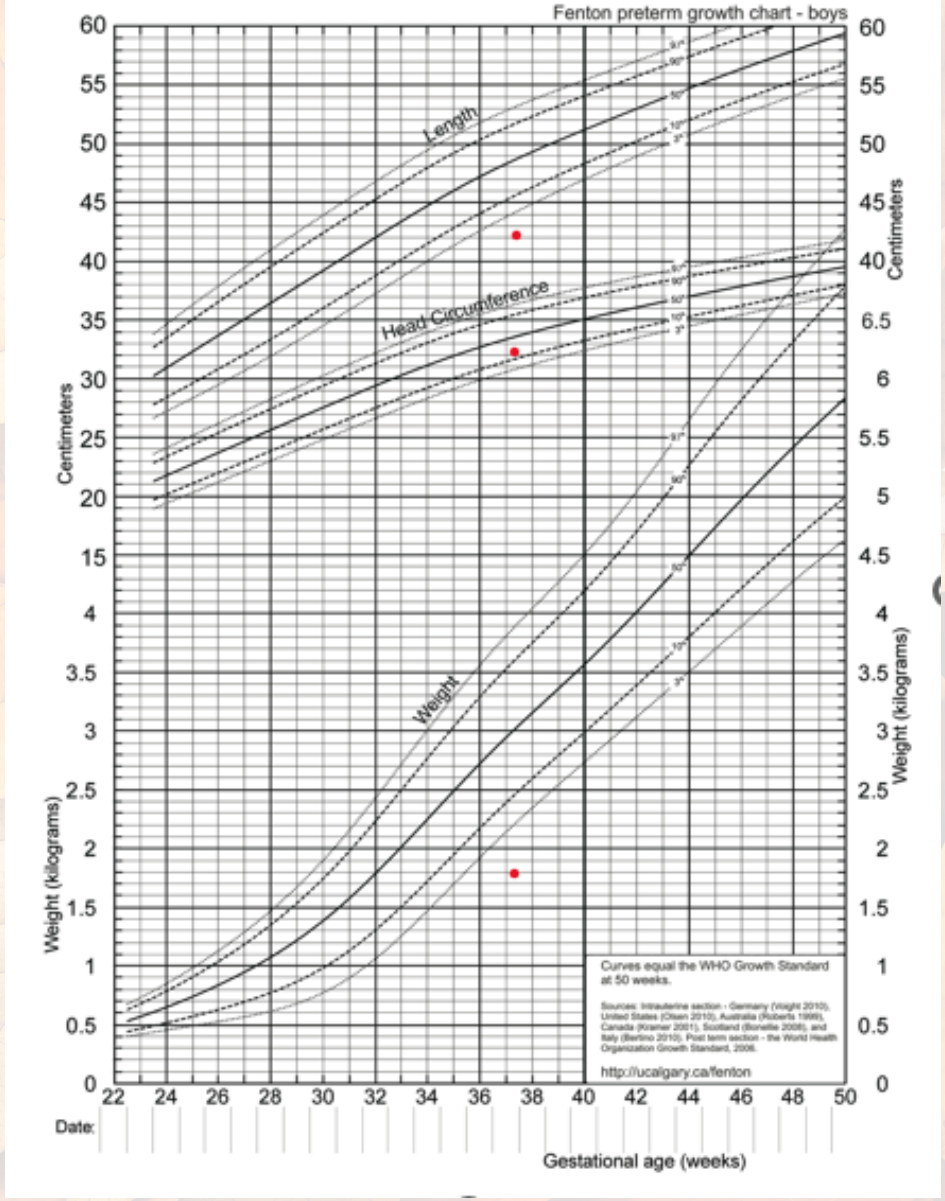
Biometrics

At 37+1w GA

- Weight: 1830g
- Lenght: 42cm
- HC: 32cm

➔ Brain sparing



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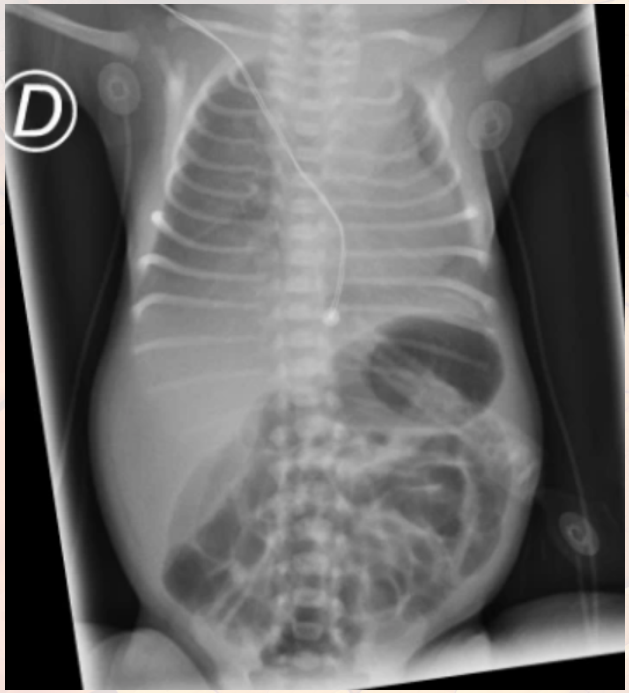
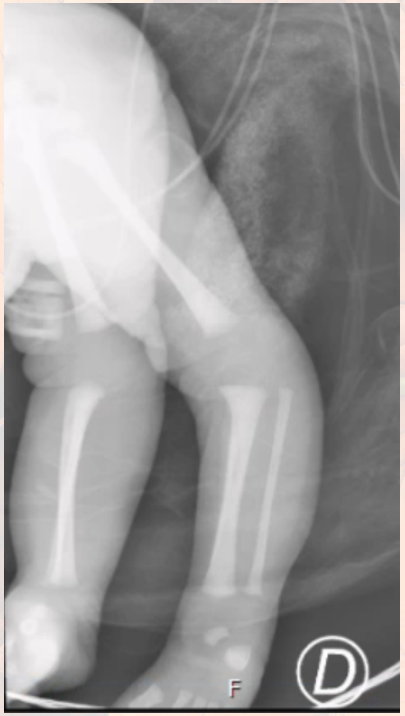
X-ray day 1

- 



- Transient tachypnea?
- CPAP PEEP 6 FiO 21%

Orthopedic evaluation:

- Luxation of knee joints
- Plaster for at least 3 weeks

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Malformation assessment first days of life

- **Blood:** Hb 15,3g/dL, WB 14000/mm³, PLT 240 000/mm³, CRP <0,6mg/L, normal kidney/liver function, normal electrolytes

- **Brain** ultrasound: normal
- **Cardiac** ultrasound: normal
- **Abdomina**l ultrasound: normal

- An email to **genetics** …

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Differential diagnosis

- Asfyxiating thoracic dystrophy (Jeune syndrome)
- Connective tissue disease (Ehlers-Danlos)
- Myopathie
- Skeletal dysplasie, dwarfism

➔ Genetics: CGH, panel thoracic dysplasia, WES in trio

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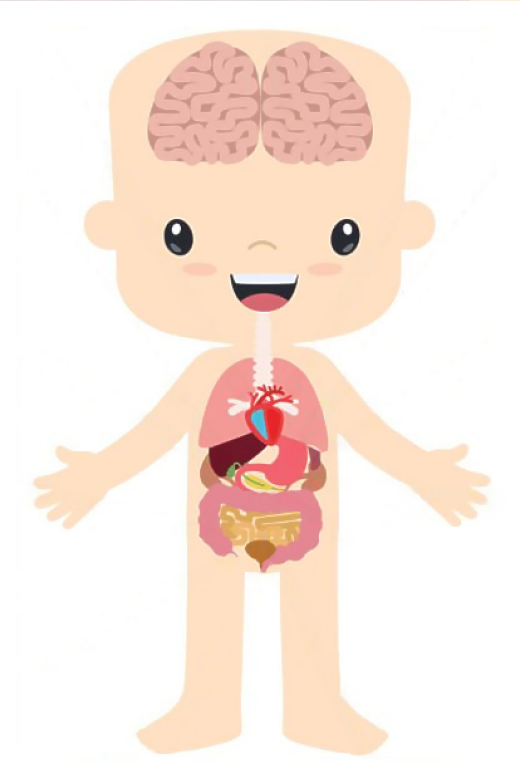
From birth till 44w GA …



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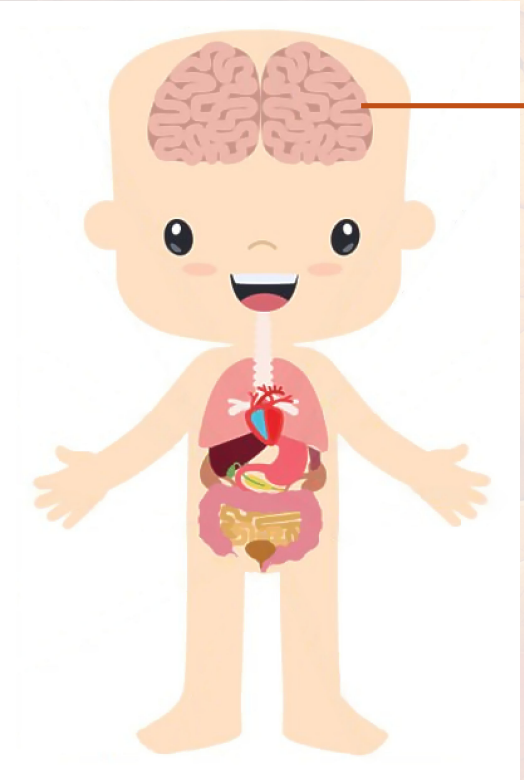

Neurological

- Ultrasound & MRI brain normal
- EEG normal
- Evaluation neurologist

→ Mild axial hypotonia, normal movements, normal reflexes, normal contact.

→ CK (day 30): normal

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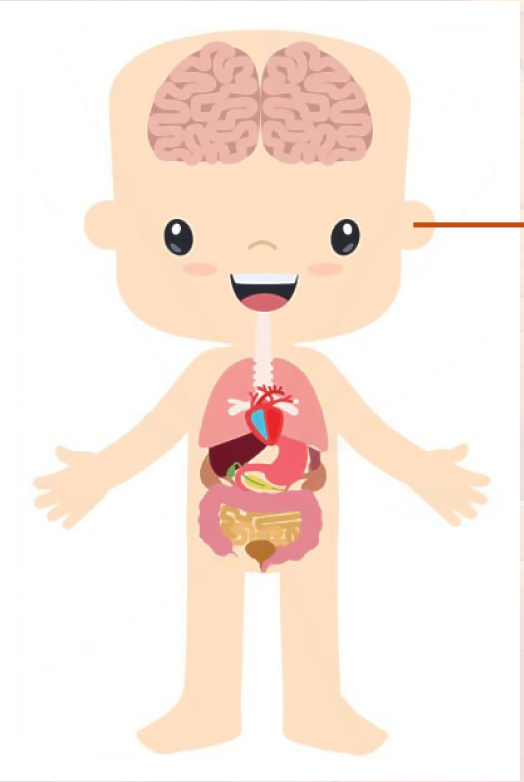
From birth till 44w GA …



ENT

- Fibroscopy normal: no laryngomalacia, no upper-airway obstruction, no cleft palate, mild GER
- BERA abnormal, thresholds 60-80dB

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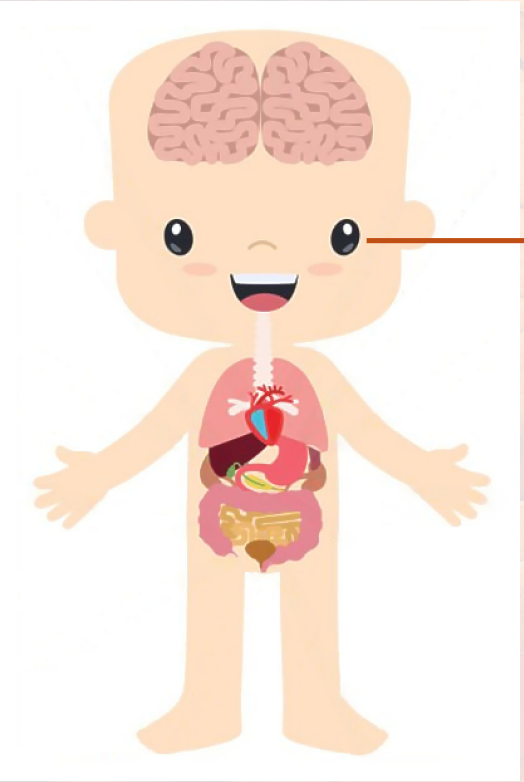

Ophtalmologic

- Evaluation normal

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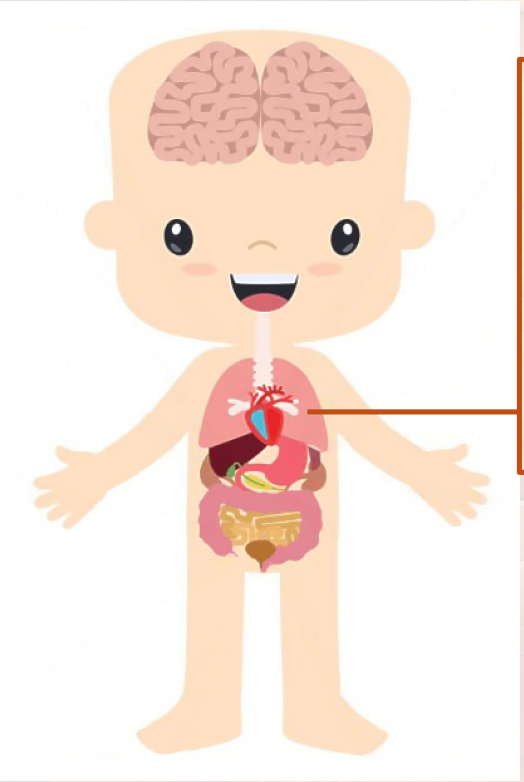


Respiratory

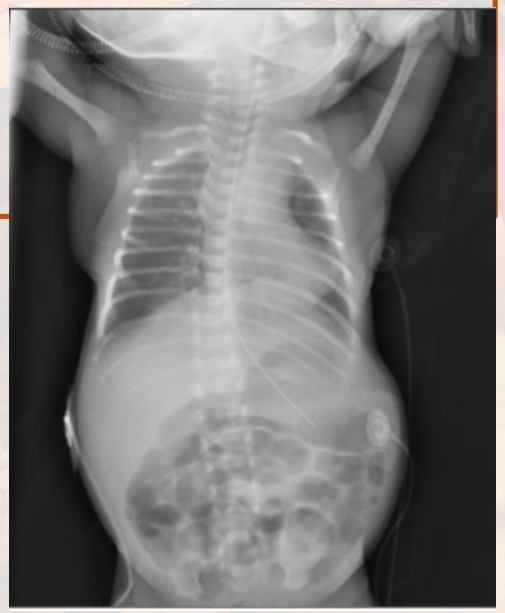
- Respiratory insufficiency

➔ Failure of high flow, need for continuous CPAP PEEP 6

➔ FiO2 21%

- X-ray day 14

- Evaluation pulmonologist



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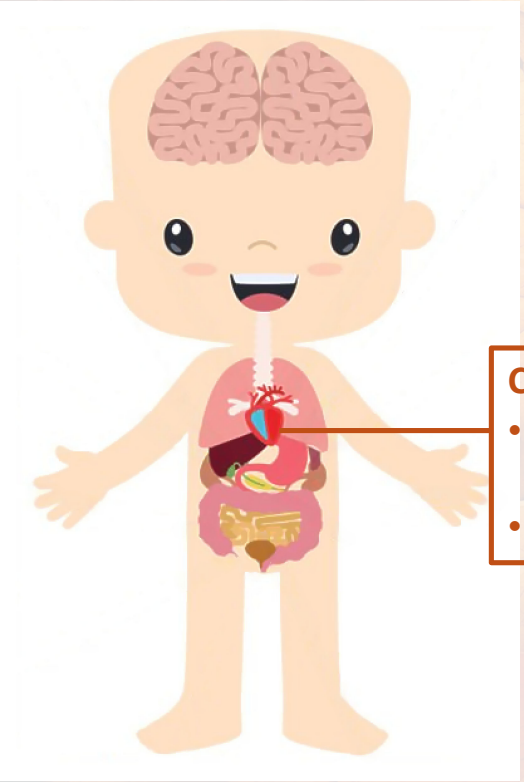

Cardiovascular

- Anatomy heart normal
- No pulmonary hypertension

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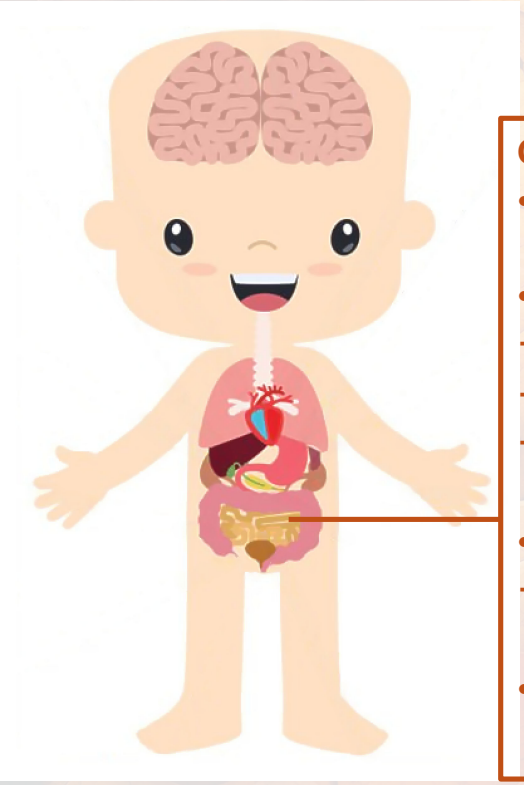


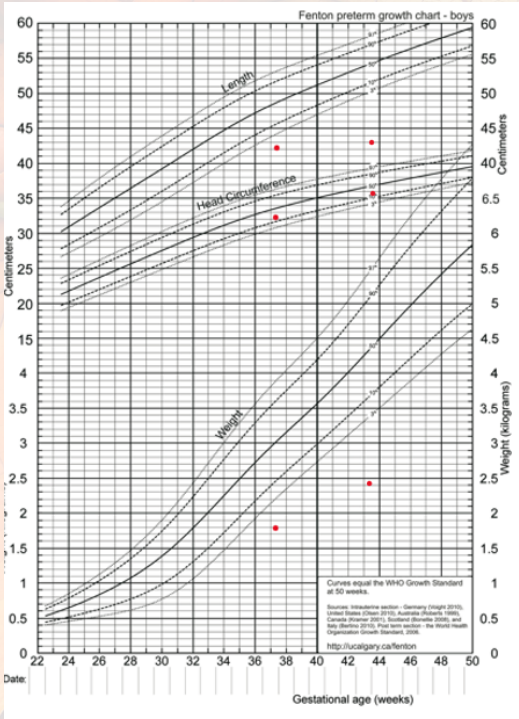
Gastro-intestinal

- Poor drinking → nasogastric tube

- Repeated regurgitations
→ Trial omeprazole: no improvement
→ ENT: mild GER
→ Continuous feeding

- Failure to thrive
→ Supplements of glucose and lipids

- X-ray: no obstruction, ultrasound: no signs of malrotation



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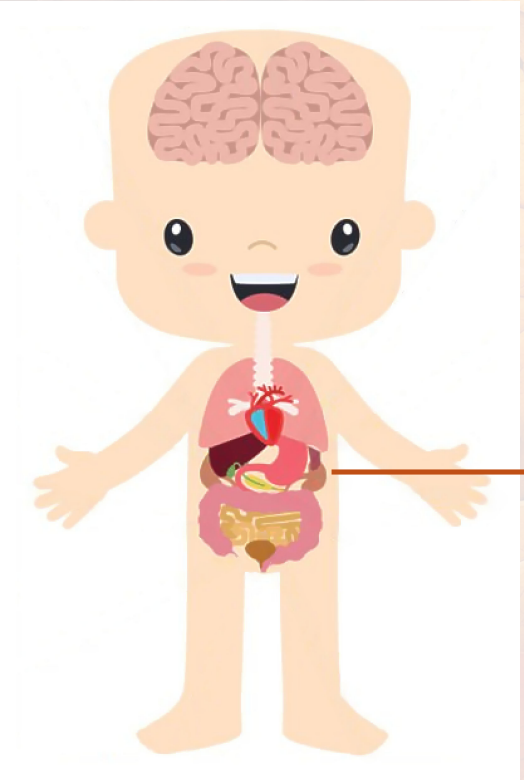

Renal & hepatic & metabolic

- Ultrasound vessie/kidneys/liver normal
- Blood normal kidney function, normal liver function
- Mild early hypocalcemia, treated with oral supplements
- 2x phototherapy, bilirubine max 18mg/dL

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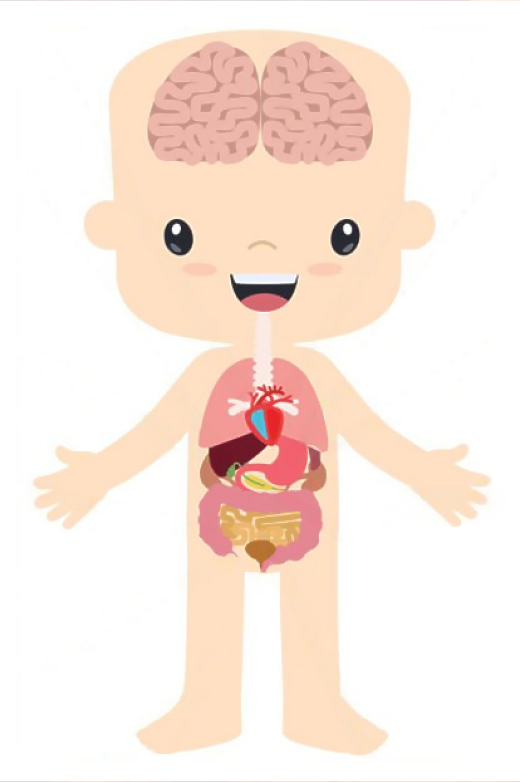

Infectious
- PCR CMV negatif

Hematology
- Normal

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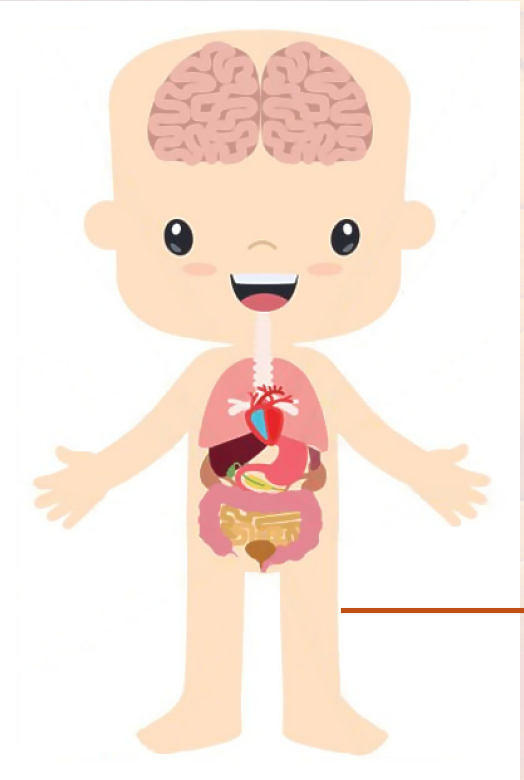
From birth till 44w GA …



Orthopedic

- 3 weeks of plaster: no luxation anymore, no further need for plaster
- Ultrasound hips: normal
- No hyperlaxity

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At 44w GA

- Persistent respiratory insufficiency

➔ need for 24h non-invasive ventilation

- Persistent gastro-intestinal difficulties

➔ probably need for gastrostomy

➔ **Transfer to paediatric ICU**

Diagnosis genetics

- CGH-array: normal male
- 21 genes analysed for thoracic dysplasia: normal
- Whole exome sequencing (WES) in trio

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Diagnosis genetics (WES)

- **Homozygote** of variant c.1A>T, p.Met1? in gene **ORC 1**
- Both parents heterozygote carriers

➔ **Meier-Gorlin syndrome (autosomal recessive)**

➔Mutation not yet described in literature

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Meier-Gorlin syndrome

- Very **rare**, <100 cases described in literature
- Mutation in **ORC 1** and 12 other different genes described - loss of function
- Pathofysiology:
  - ➢ not well understood
  - ➢ disturbed DNA-replication → decreased cell proliferation → **diminished overall growth**
- Also called **ear-patella short stature** syndrome
- Characteristics:

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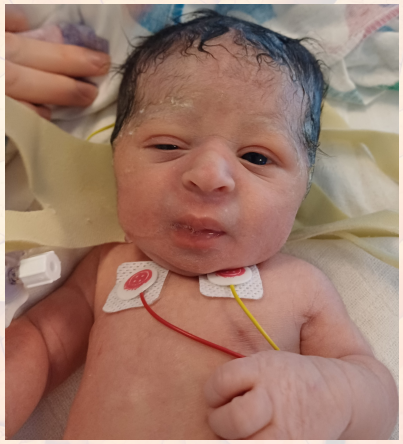
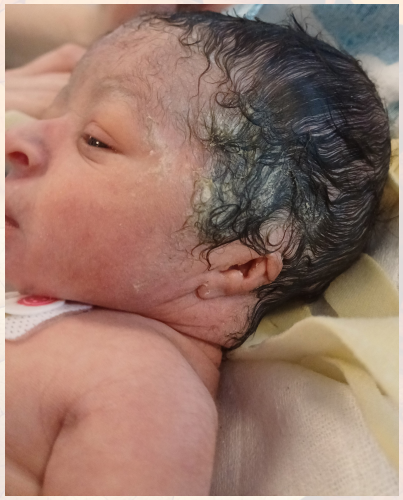
Table 1 Clinical features of 35 individuals with Meier–Gorlin syndrome with biallelic mutations in one of the five pre-replication genes and 10 individuals with a clinical diagnosis of Meier–Gorlin syndrome without a definitive molecular diagnosis, including one individual with a monoallelic mutation in *ORC1* and two with a monoallelic mutation in *CDT1*

Clinical characteristics	*Total (35 individuals)*
Sex ratio M/F	14 M/21 F
Average age at examination	12 y 9 m
Range age at examination	3 m–47 y
Classical triad of clinical features	
Short stature (height for age <−2 SD)	31/35 (89%)
Microtia	34/35 (97%)
Patellar hypoplasia/aplasia	30/32 (94%)
Growth (represented in mean SD)	
Birth weight (SD range)	−3.8 SD (< −6.5 to −0.3
IUGR (birth weight <−1.3 SD)	32/33 (97%)
Height at examination (SD range)	−4.4 SD (−9.6 to −0.4)
Weight at examination (SD range)	−3.9 SD (−9.3 to 0.8)
Head circumference (SD range)	−2.9 SD (−9.8 to 1.7)
Microcephaly (OFC for age <−3 SD)	13/29 (45%)
Disproportionate stature	4/17 (24%)
Facial features	
Abnormally formed ears	19/29 (66%)
Low-set ears	16/28 (57%)
Posteriorly rotated ears	7/17 (41%)
Convex nasal profile	7/14 (50%)
Narrow nose	8/16 (50%)
High nasal bridge	10/17 (59%)
Microstomia	18/29 (62%)
Full lips	21/30 (70%)
Micro-/retrognathia	25/29 (86%)
Downslanted palpebral fissures	9/17 (53%)
Neurological	
Intellectual disability	1/31 (3%)
Delayed motor development	6/32 (19%)
Delayed speech development	5/32 (16%)





Munnik et al. 2012

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	Total (35 individuals)
Respiratory tract	
Respiratory problems during infancy	11/23 (48%)
Pulmonary emphysema	12/28 (43%)
Tracheomalacia	8/24 (33%)
Laryngomalacia	6/24 (25%)
Bronchomalacia	4/24 (17%)
Cardiac anomalies	2/30 (7%)
Gastrointestinal	
Feeding problems during infancy	26/32 (81%)
Nasogastric feeding/gastrostomy	11/31 (35%)
Failure to thrive	11/31 (35%)
Gastroesophageal reflux	13/31 (42%)
Urogenital anomalies	
Abnormal genitalia	15/35 (43%)
Hypospadias	1/14 (7%)
Cryptorchidism/small testes	9/14 (64%)
Micropenis	2/14 (14%)
Clitoromegaly	2/21 (10%)
Hypoplastic labia minora/majora	5/21 (24%)
Renal anomalies	3/35 (9%)
Secondary sexual characteristics	
Mammary hypoplasia	10/10 (100%)
Absent/sparse axillary hair	7/8 (88%)
Absent/sparse pubic hair	1/6 (17%)
Growth hormone treatment	10/25 (40%)
Musculoskeletal anomalies	
Delayed bone age	14/22 (64%)
Genu recurvatum	9/28 (32%)
Contractures/club feet	5/27 (19%)
Other	

Munnik et al. 2012

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Respiratory insufficiency?

Respiratory tract	
Respiratory problems during infancy	11/23 (48%)
Pulmonary emphysema	12/28 (43%)
Tracheomalacia	8/24 (33%)
Laryngomalacia	6/24 (25%)
Bronchomalacia	4/24 (17%)

Literature?

- No patients described as severly affected as our case
- 4 lethal cases described with Meier-Gorlin, all 4 with lung emphysema

➔ **CT thorax: no signs of emphysema,** otherwise normal

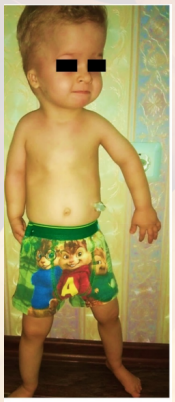
➔ ENT: no laryngomalacia

➔ No bronchoscopy done

Musculoskeletal anomalies	
Delayed bone age	14/22 (64%)
Genu recurvatum	9/28 (32%)
Contractures/club feet	5/27 (19%)
Other	

Literature?

- Slender ribs described, muskuloskeletal dysplasia
- 1 case where a diagnosis of Jeune syndrome was suspected



Nazarenko et al. 2021

➔ **Suspicion of restrictif lung disease due to dysplastic small thorax**

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How is our patient doing in the meanwhile?

- **Deteriorating respiratory insufficiency** (CPAP → BIPAP)
- **No improvement on gastro-intestinal level**, poor drinking, need for naso-jejunal tube to control vomiting
- **Prognosis?** Based on actual clinic**: poor.**
- Difficult social situation

➔Decision of **limitation of therapy**

- 3 weeks later, at the age of **3,5 months**: intestinal perforation (naso-jejunal tube)

➔ Pluridisciplinar decision not to operate, only comfort care ➔ **passes away**

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Take home messages

- **Meier-Gorlin**: IUGR-microtia – patellar hypo/aplasia
- IUGR and consanguinity → really '**just' IUGR?**
- Importance of **publication** of (rare) cases

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Thank you!

Dank u!

Merci!

Questions?

Literature

- Munnik et al. Meier-Gorlin syndrome. Orphanet J Rare Dis. 2015 Sep 17;10:114.
- Munnik et al. Meier-Gorlin syndrome genotype-phenotype studies: 35 individuals with pre-replication complex gene mutations and 10 without molecular diagnosis. Eur J Genet. 2012 Jun,20(6):598-606.
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- Nielsen-Dandoroff et al. The expanding genetic and clinical landscape associated with Meier-Gorlin syndrome. Eur J Hum Genet. 2023 Aug;31(8):859-868.

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