Hyperinsulinism guidelines and diagnosis

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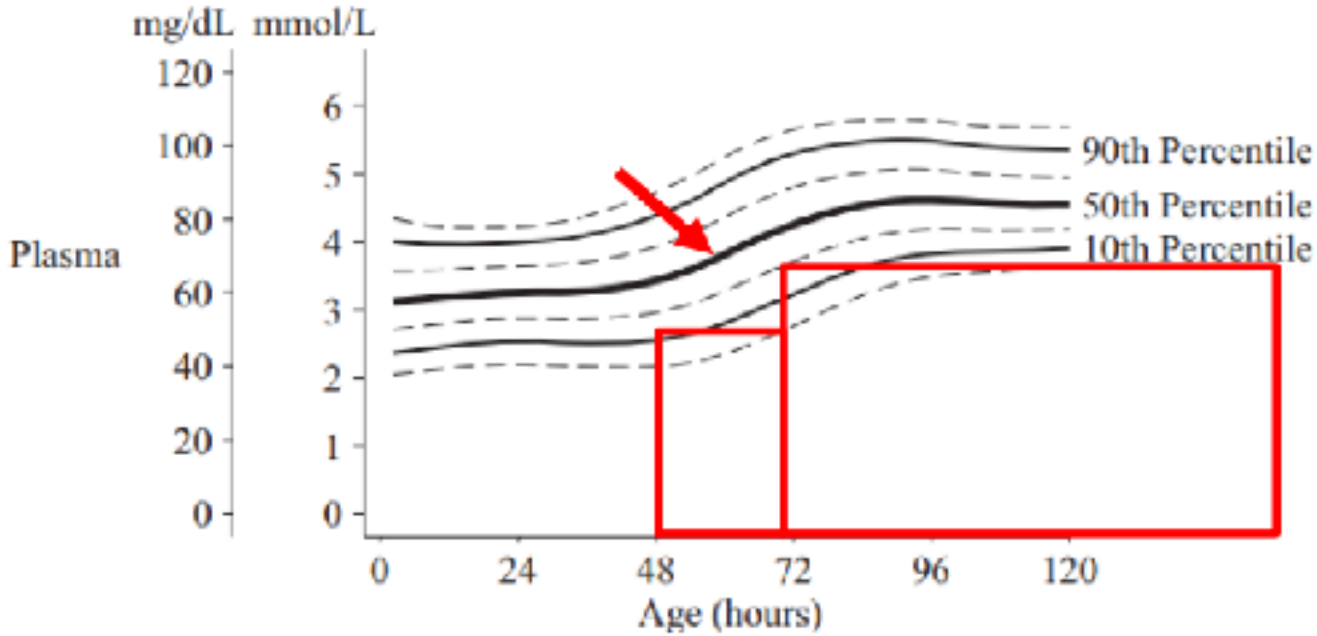
CHI family conference
Marseille, Sept. 4, 2026

International hyperinsulinism center, Hans Christian Andersen Children's Hospital, Odense University Hospital, Denmark

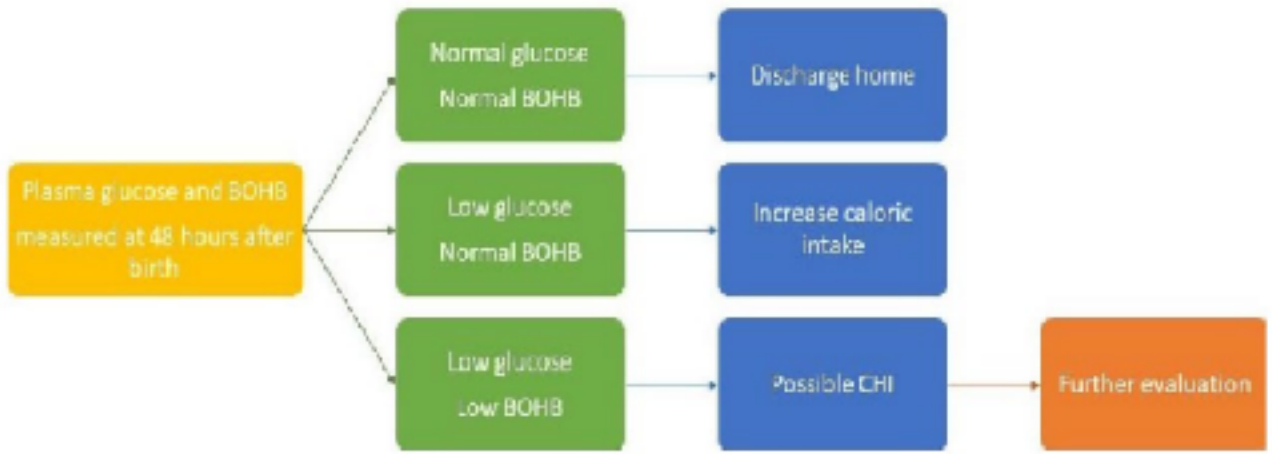
100 international patients Nov. 2023

+ DNA from more than 20 countries (n> 400)

No screening or diagnosis of HI before age 2-3 days

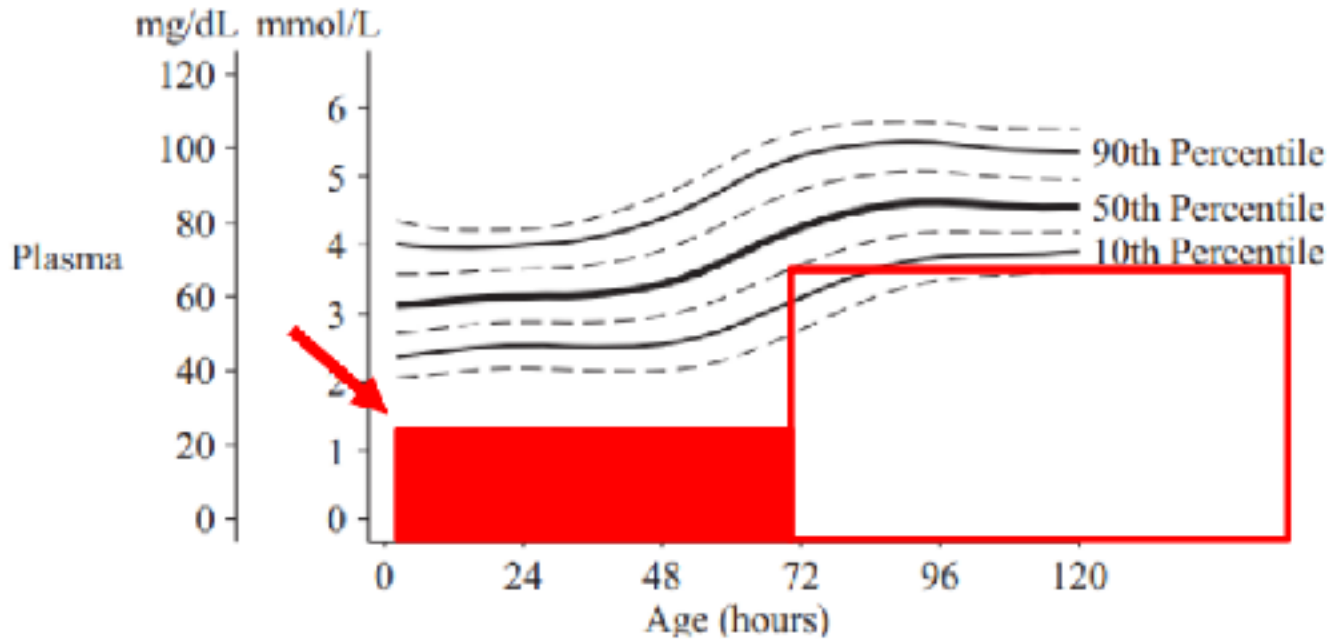


HI screening for all, proposal: G+BOHB <3.0 mM at 48 h



Kaiser, J Clin Med 2024

Problem: HI may be severe and un-/ undertreated from a few hours of age



Wilma: ”help, I’m low”

GA 38+2, BW 4100 g. P-glucose 0.3 mmol/L 6 hours old

Macrosomic, LGA

Gestational age 39+5, BW 5650 g, 57 cm

2- hour glucose screen: 0.1 mmol/L

No maternal diabetes or obesity

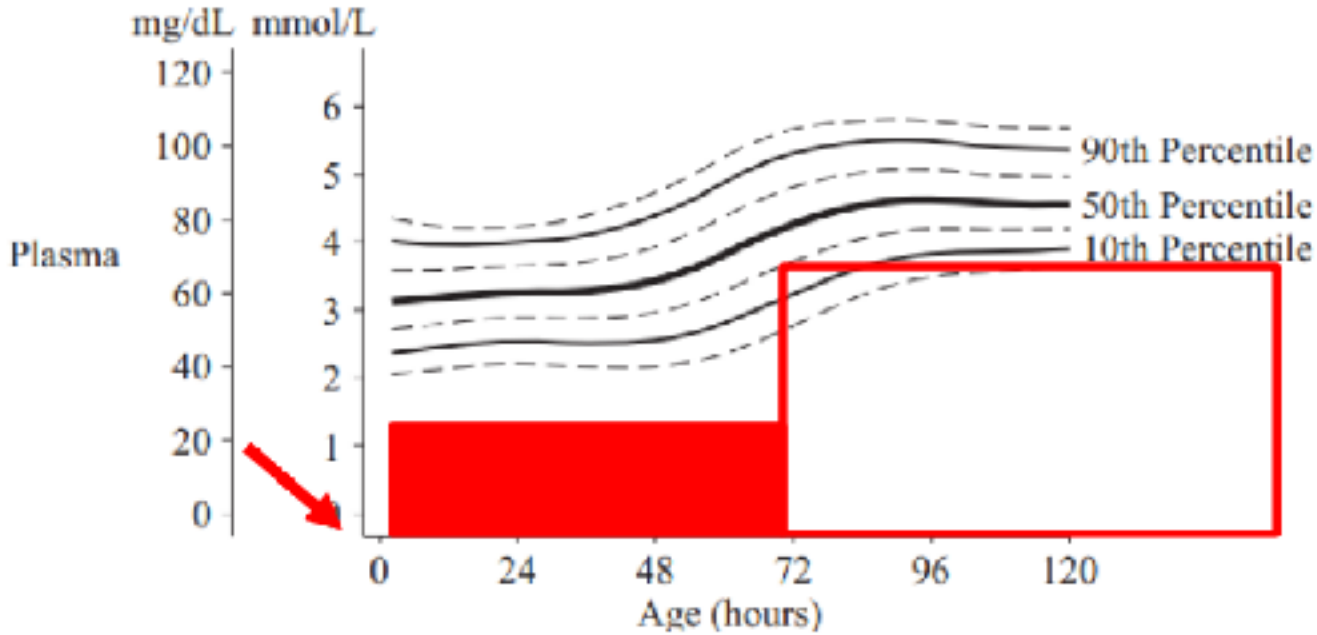
Rasmus

- Term Danish boy, uncomplicated delivery, 3rd child, no hypoglycemia risk, normal BW
- 2 hours old uneasy
- Bedside glucose ”low”
- ”Glucometer failure”
- Sent home 5-6 hours old!

Rasmus

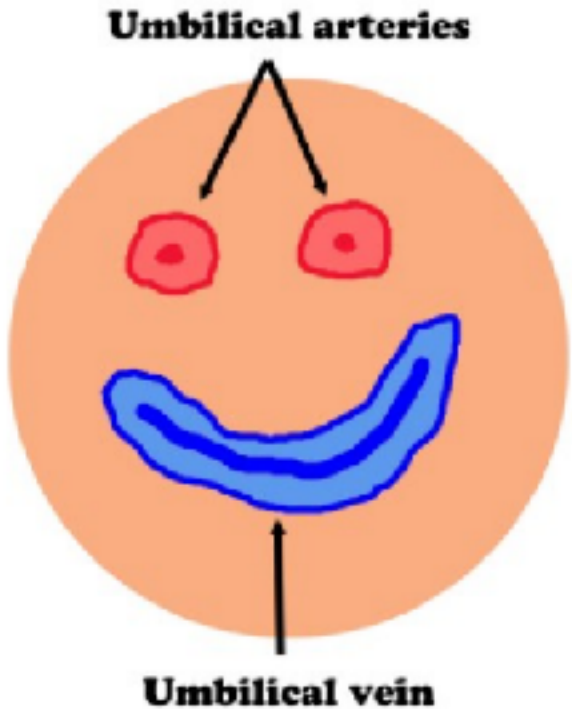
- Admitted age 2 days with convulsions and unconsciousness
- Glucometer 1: ”low”
- Glucometer 2: 0.0 mmol/L
- Iv glucose, HI diagnosed, since then well treated
- Damage done
  - 9 y-old retarded, epilepsy, cerebral palsy

HI may be severe and un/undertreated from a few hours of age



Earliest possible universal screening?

National study Denmark:
Umbilical cord glucose to screen for HI



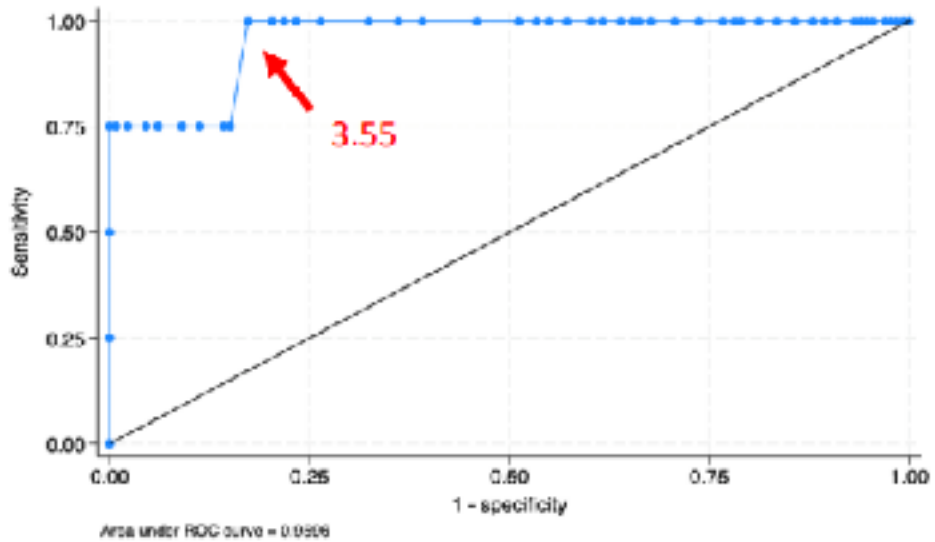
Julie Siersbæk, Phd study

Cord values, 4 cases vs controls

	Healthy	Hyperinsulinism	P
Patient number	133	4	
Venous pH, mean (range)	7.34 (7.14-7.48)	7.3 (7.24-7.36)	0.1139
Arterial pH, mean (range)	7.24 (7.05-7.38)	7.18 (7.1-7.24)	0.1216
Venous BE, mean (range)	-3.84 (-10.2-3.5)	-1.75 (-3.3 – 1.1)	0.0531
Arterial BE, mean (range)	-3.09 (-11.8-2.5)	-1.33 (-3.3-1.3)	0.1480
Venous Glucose, mmol/L, mean (range)	**5.81 (3.4-9.2)**	**3.85 (3.4-4.8)**	**0.0019**
Arterial Glucose, mmol/L, mean (range)	**4.72 (2.5-7.9)**	**2.15 (0.6-3.5)**	**<0.0001**
Delta Glucose, mmol/L, mean (range)	**1.08 (0-3.6)**	**1.7 (1.1-2.8)**	**0.0365**

Julie Siersbæk, PhD study

National study, screening for all: Cord arterial glucose <3.5 mM



True positive rate: 100%
False positiv rate: 17%

Julie Siersbæk, PhD study

Clues to diagnosing HI

- Macrosomia at birth (insulin), no maternal diabetes or obesity
- Unexpected severe hypoglycemia (also day 1)

Clues to diagnosing HI

- Macrosomia at birth (insulin), no maternal diabetes or obesity
- Unexpected severe hypoglycemia (also day 1)
- No quick remission (exeeding day 3 of life)
- A glucose demand exceeding 8 mg/kg/minute
- No/low ketone bodies *during hypoglycemia*
- Inappropriately large glycemic response to glucagon (≥1.7 mmol/L)

Hyperinsulinemic Hypoglycemia

Definition: Hypoglycemia with inappropriately elevated p-insulin

Glukose;B	mmol/L	3.1	11.0	5.2	3.3	2.6
Glukose;P	mmol/L	3.1	11.0	5.3	3.4	2.7
Glukose;P(kB)	mmol/L	3.1	11.0			
Hæmoglobin A1c (IFCC) - POCT;Hb(B)	mmol/mol					
Hæmoglobin A1c (IFCC);Hb(B)	mmol/mol		<48			
Glukose, middel (fra HbA1c) -POCT;P	mmol/L					
Glukose, middel (fra HbA1c);P	mmol/L					
Insulin;P	pmol/L			ⓘ 162	ⓘ 16	ⓘ 20
Insulin;P(fPt)	pmol/L	18	173			

At plasma glucose <2.8 mmol/L: plasma insulin >1.25 µU/mL (8.7 pmol/L)

De Ionlay, Intern. Guideline, Horm Res 2023

Diagnosing HI –sensitive insulin assay

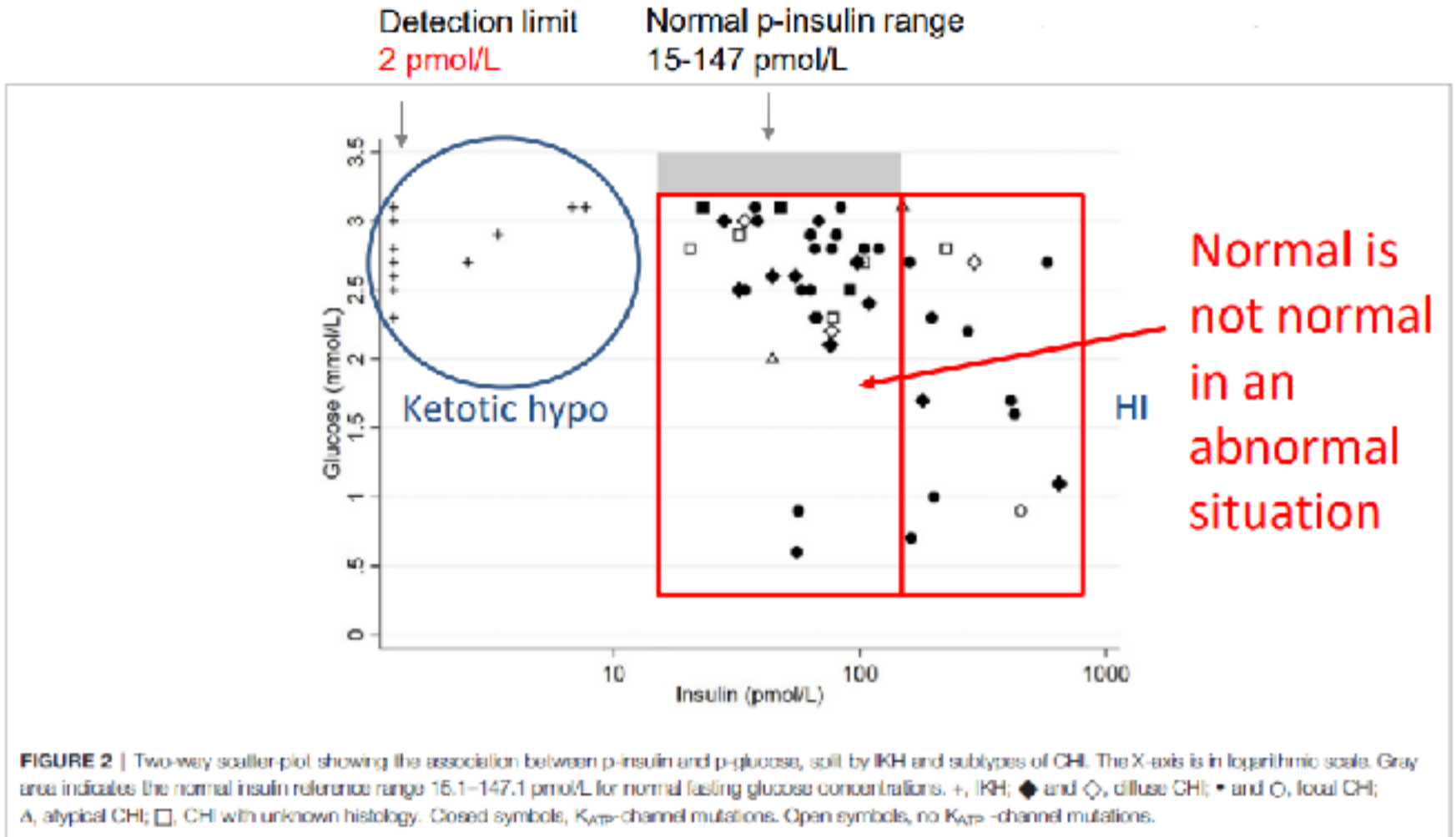


FIGURE 2 | Two-way scatter-plot showing the association between p-insulin and p-glucose, split by IKH and subtypes of CHI. The X-axis is in logarithmic scale. Gray area indicates the normal insulin reference range 15.1–147.1 pmol/L for normal fasting glucose concentrations. +, IKH; ◆ and ◇, diffuse CHI; • and ○, focal CHI; A, atypical CHI; □, CHI with unknown histology. Closed symbols, K_{ATP}-channel mutations. Open symbols, no K_{ATP} -channel mutations.

Siersbæk et al, Front Endocrinol 2021

Get the critical sampling during hypoglycemia!

Typical HI presentation

- P-glucose, bedside + central lab
- Blood ketones/BOBH bedside
- P-insulin (C-peptide)

Broader approach

- P-glucose (bedside + central lab)
- P-insulin (C-peptide, proinsulin)
- Blood ketones (BOBH bedside)
- Acid/base +lactate
- (FFA)
- P-GH, p-cortisol
- (p-ammonia)
- (p-amino acids)
- (u-metabolic screening)

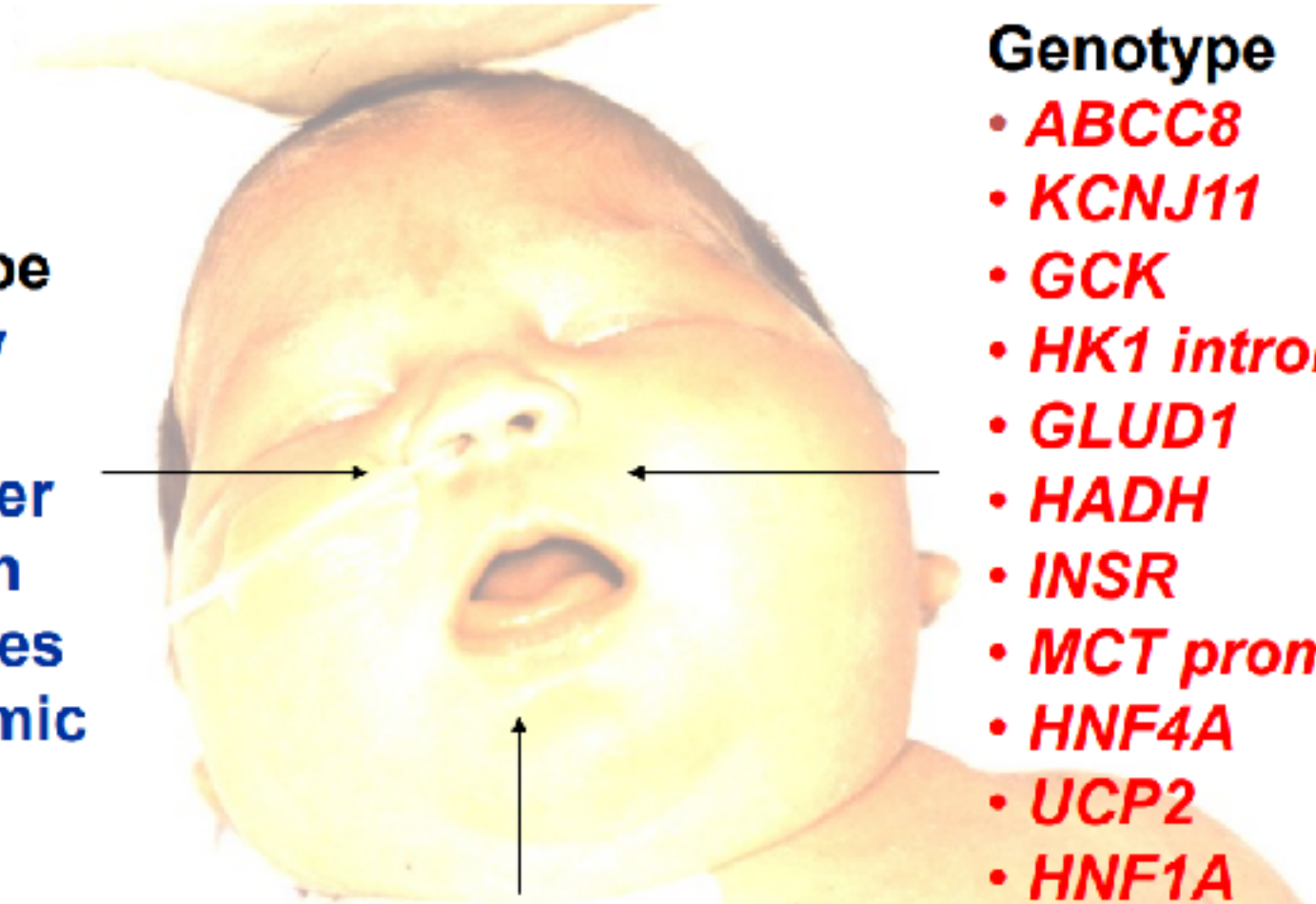
Get the critical sampling !

- If not actual hypoglycemia:
  - Fasting hypoglycemia provocation
    - I.v. catheter
    - Close bedside BG monitoring
    - Critical sampling when BG <2.8 mM

HI subtyping – improve treatment

Phenotype
- **severity**
- **onset**
- **character**
- **duration**

→ **diabetes**
- **syndromic**



Histology

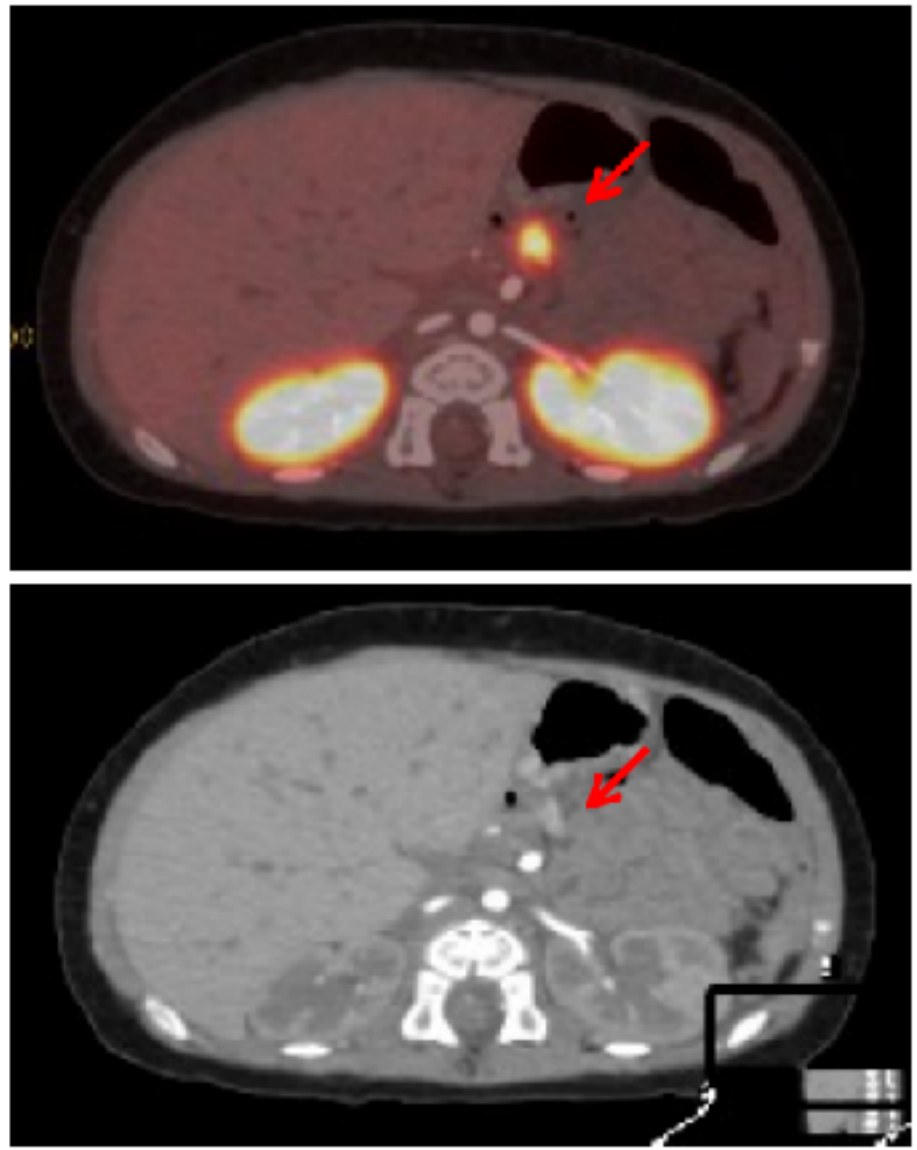
Diffuse, focal, atypical

Genotype
- ***ABCC8***
- ***KCNJ11***
- ***GCK***
- ***HK1 intron 2***
- ***GLUD1***
- ***HADH***
- ***INSR***
- ***MCT promotor***
- ***HNF4A***
- ***UCP2***
- ***HNF1A***
- ***PGM1***
- ***PMM2***

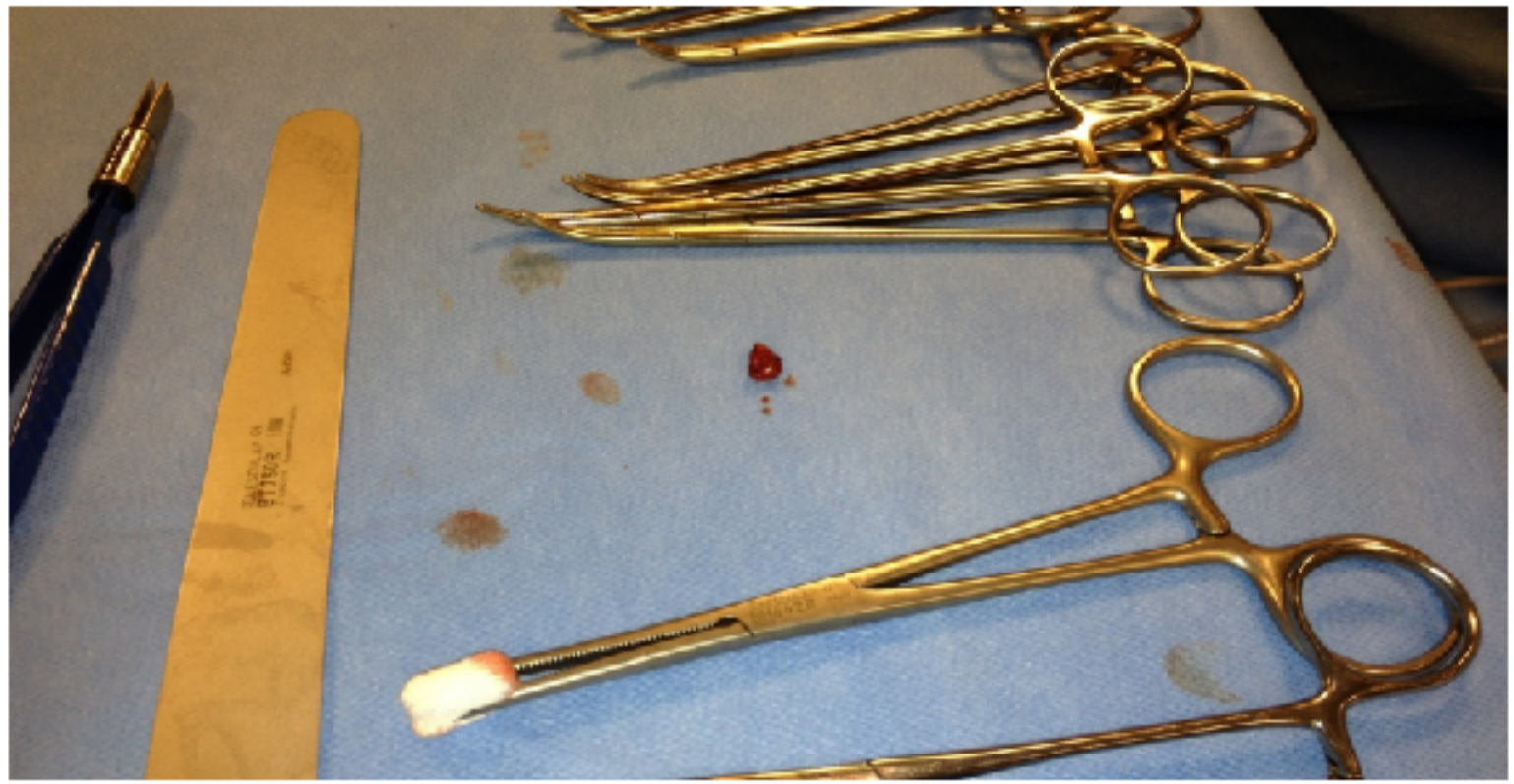
Margarita, Ukraine, 2½ m

Paternal *ABCC8* mutation

Margarita, Ukraine



Margarita, Ukraine



- Cured by focal lesion enucleation

Margarita, follow up