Congenital Hyperinsulinism Case Studies: variability of phenotype and response to medical therapy

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Patient 1.

- 20 months old boy

- <u>personal history:</u>
  born at 37 weeks of gestational age by cesarean section.
Birthweight: 4300 g. No complications during pregnancy

- history of hypoglycaemia detected on the 2nd day of life, and a continuous intravenous glucose supplementation as well as oral feeding were required to keep his blood glucose in the normal range
- congenital hyperinsulinism was laboratory confirmed

- <u>physical examination:</u>
  at presentation at the age of 20 months he weighed 17,2 kg (>97th p.) and was 87 cm tall (50th p.) BMI: 22,7 kg/m^2 (>97th p.)
  no other abnormal findings

Patient 1.

The molecular genetic analysis for hyperinsulinism at the Molecular Genetics Laboratory of the University of Exeter Medical School revealed:

a compound heterozygous mutation in the exons 28 and 37 of the ***ABCC8*** gene (ATP binding cassette subfamily C member 8), c.3512del inherited from his father and a previously reported missense mutation p.R1494W inherited from his mother.

Thus the diagnosis of recessively inherited congenital hyperinsulinism was genetically confirmed.

Patient 1.

<u>therapy modifications:</u>

- therapy with diazoxide started in the first days of life but was not efficient
- at the age of 1 month started continuous glucagon infusion with octreotide
- at the age of 3 months diazoxide was stopped
- at the age of 7 months sirolimus treatment was started and glucagon was stopped: at this age his therapy consisted of octreotide (Sandostatin 15 µg sc every 27d, 32,3 µg/kg/d) and sirolimus (2mg/d, 116 µg/kg/d), he also required continuous feeding through a gastrostomy tube

Patient 1.

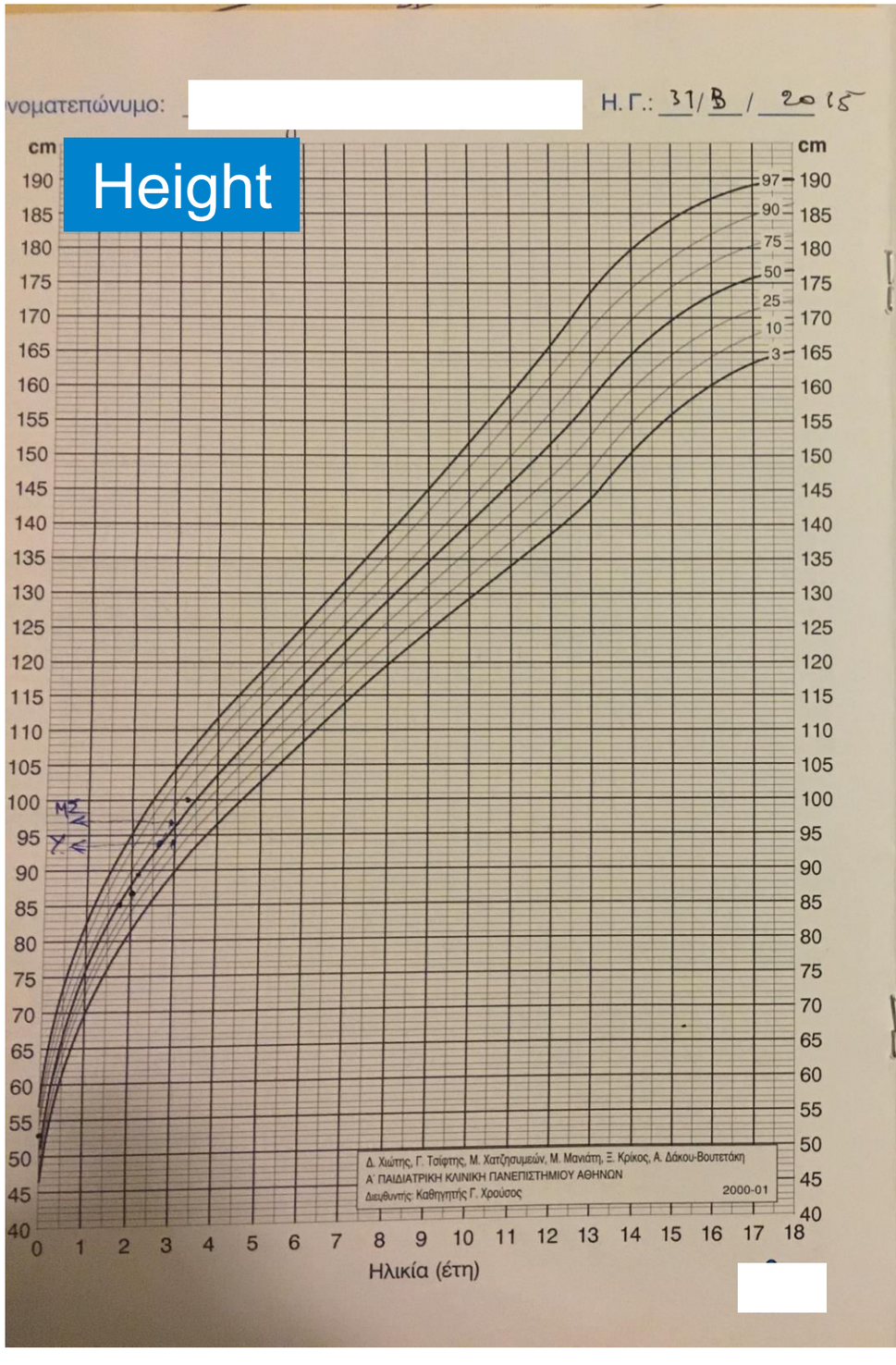
<u>therapy modifications:</u>

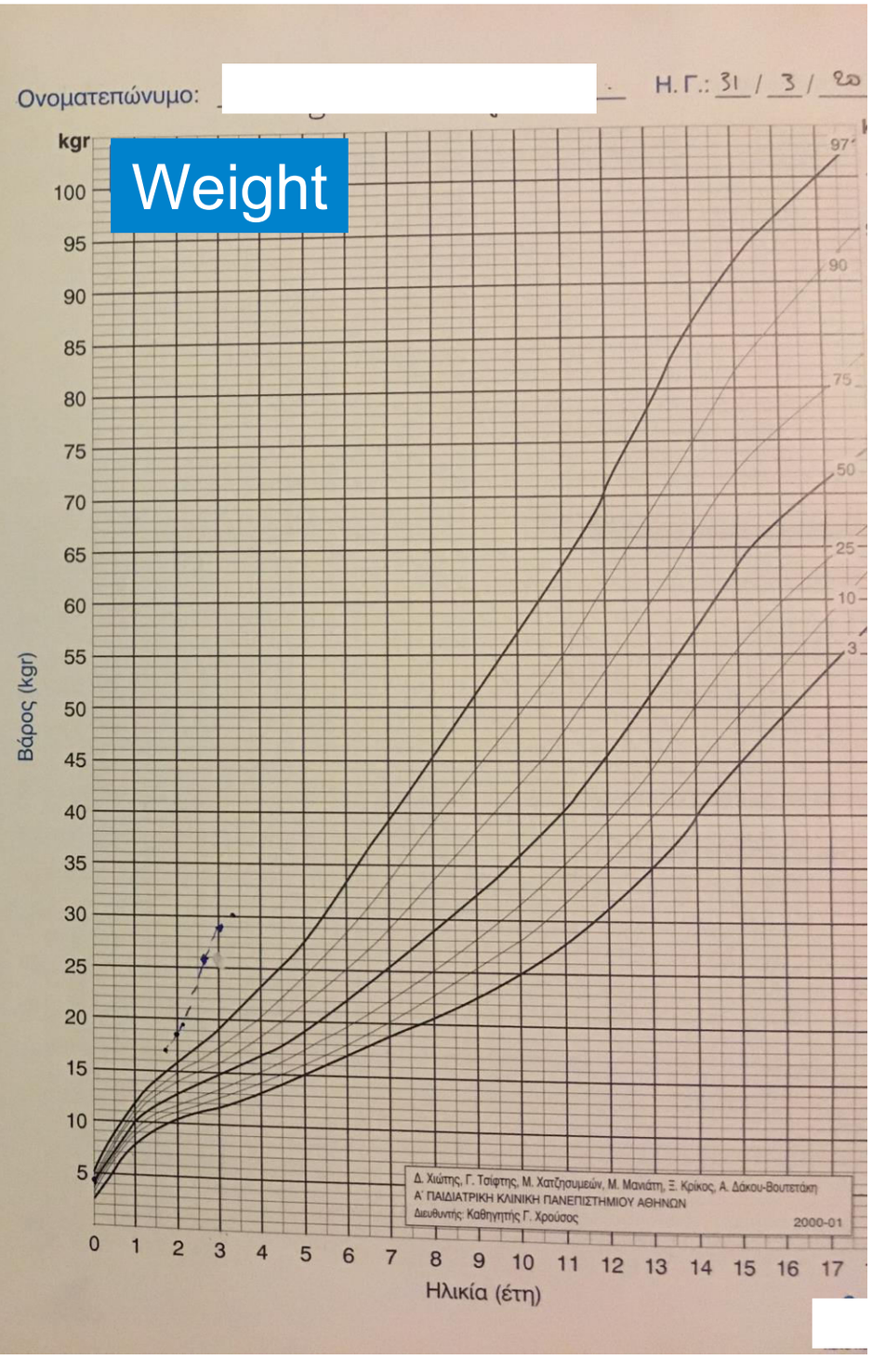
- at the age of 2 3/12 years it was possible to reduce the sirolimus treatment to 1,5mg/d (77 µg/kg/d) without increasing octreotide dose (28,6 µg/kg/d)
- at the age of 2 5/12 years sirolimus was stopped, octreotide 20 mg sc every 24d (37 µg/kg/d)

required continuous feeding through gastrostomy tube during the night as well as corn flour with his meals (10-30g 5x/d) as substitution with carbohydrates

Patient 1.

Growth chart





Patient 1.

- he is now 3 years old, weights 30,2 kg (>97th p.)

- he is being followed up at our outpatient department and has been found to be euglycemic (min Glu 68 mg/dl) under Octreotide (20 mg Sandostatin every 22-27 days, 24,5 - 30,1 μg/kg/d)

- he still requires continuous feeding through his gastrostomy tube during the night (milk 48 ml/h from 12 am to 07 pm) as well as corn flour with his meals (10g 5x/d)

- because of this intense feeding he has gained excessive weight.
- his growth and psychomotor development though are adequate for his age

Patient 2.

- 10 months old boy

- <u>personal history:</u>
  born at 40 weeks of gestational age by vaginal delivery
  no illnesses, no medication

- <u>social history:</u> first son of healthy non-consanguineous parents, single mother

- presented twice in one month: loss of consciousness, hypotonia and upward rolling of the eyes
  reduced food intake and weight loss

- <u>physical examination:</u>
  at presentation he weighed 9,7 kg (25-50th p) and was 78 cm tall (50-75th p)
  no abnormal findings

Patient 2.

- <u>during hospitalisation:</u>
  - repeatedly episodes with hypoglycaemia (not possible to take the critical sample)
  - fasting test (after 16h): Glu 28 mg/dl, Insulin 2,2 µIU/mL, Cortisol 23,35 µIU/mL, negative ketonuria
  - hypoglycaemic episodes with inappropriately low normal, not suppressed levels of insulin and without ketonuria, thus the diagnosis of hyperinsulinism was confirmed

- he required a high intravenous glucose infusion rate was required without achieving normoglycemia
- after three weeks oral diazoxide was started progressively from 5 to 15 mg/kg/d and iv glucose requirements were decreased
- Hydrochlorothiazide was added without effective response

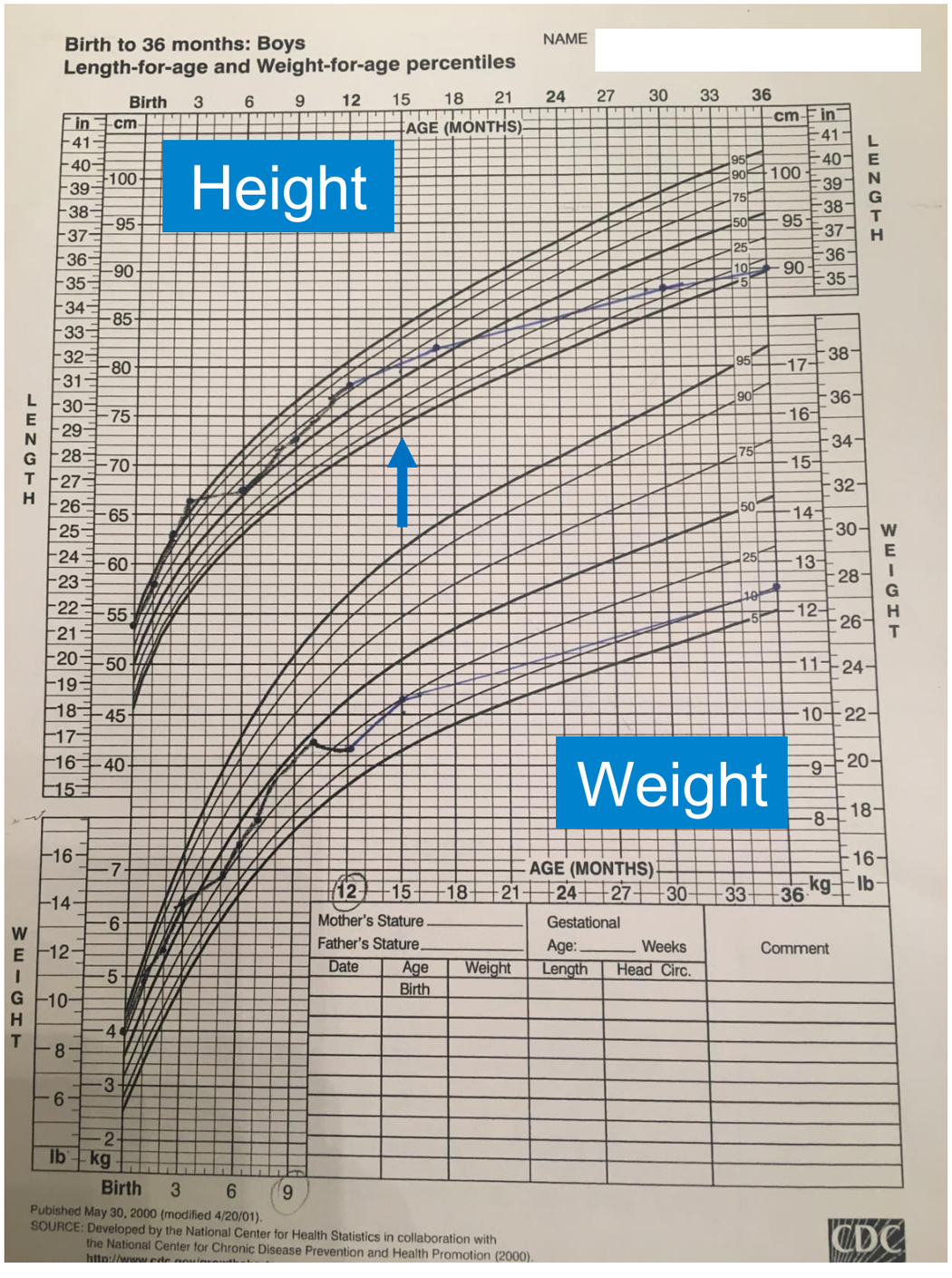
Patient 2.

The molecular genetic analysis for hyperinsulinism at the Molecular Genetics Laboratory of the University of Exeter Medical School revealed:
a heterozygous nonsense mutation in the exon 8 of the ***ABCC8*** gene (ATP binding cassette subfamily C member 8) c.1290G>A p.Trp430Ter (p.W430*) previously reported.
The mutation was not detected in his mother. It was not possible to obtain a DNA analysis of the father.

- after receiving the results of the genetic analysis octreotide was started at the age of 15 months (10 mg Sandostatin every 20d, 49 µg/kg/d)
  It was then possible to stop the rest medication and the iv glucose infusion.

Patient 2.

Growth chart



Patient 2.

- he is now 3,5 years old

- he is now being followed up at our outpatient department and has been found to be euglycemic under Octreotide (10 mg Sandostatin every 6-8 weeks, 13,7 - 18,3 µg/kg/d)

- demonstrated high TSH values (max. 19,39 mIU/l) with negative thyroid auto-antibodies and a substitution therapy with thyroxine (25 µg/d) was initiated

- he remains eutrophic and has normal psychomotor development however, he has shown a delay in his growth development as a result of the octreotide treatment

Patient 3.

- 14-months-old boy

- <u>personal history:</u>
  full term infant born by normal delivery. Birthweight: 3250 g.
  no complications during pregnancy

- history of hypoglycaemia
  initially presented with seizure activity secondary to severe hypoglycaemia
  hyperinsulinism diagnosed at 7 months of age
- therapy: diazoxide 60 mg/d (6,9 mg/kg/day)

- <u>physical examination:</u>
  at presentation he weighed 8,6 kg (75^{th} p.) and was 75 cm tall (10^{th} p.)
  generalised hypertrichosis, no other abnormal findings

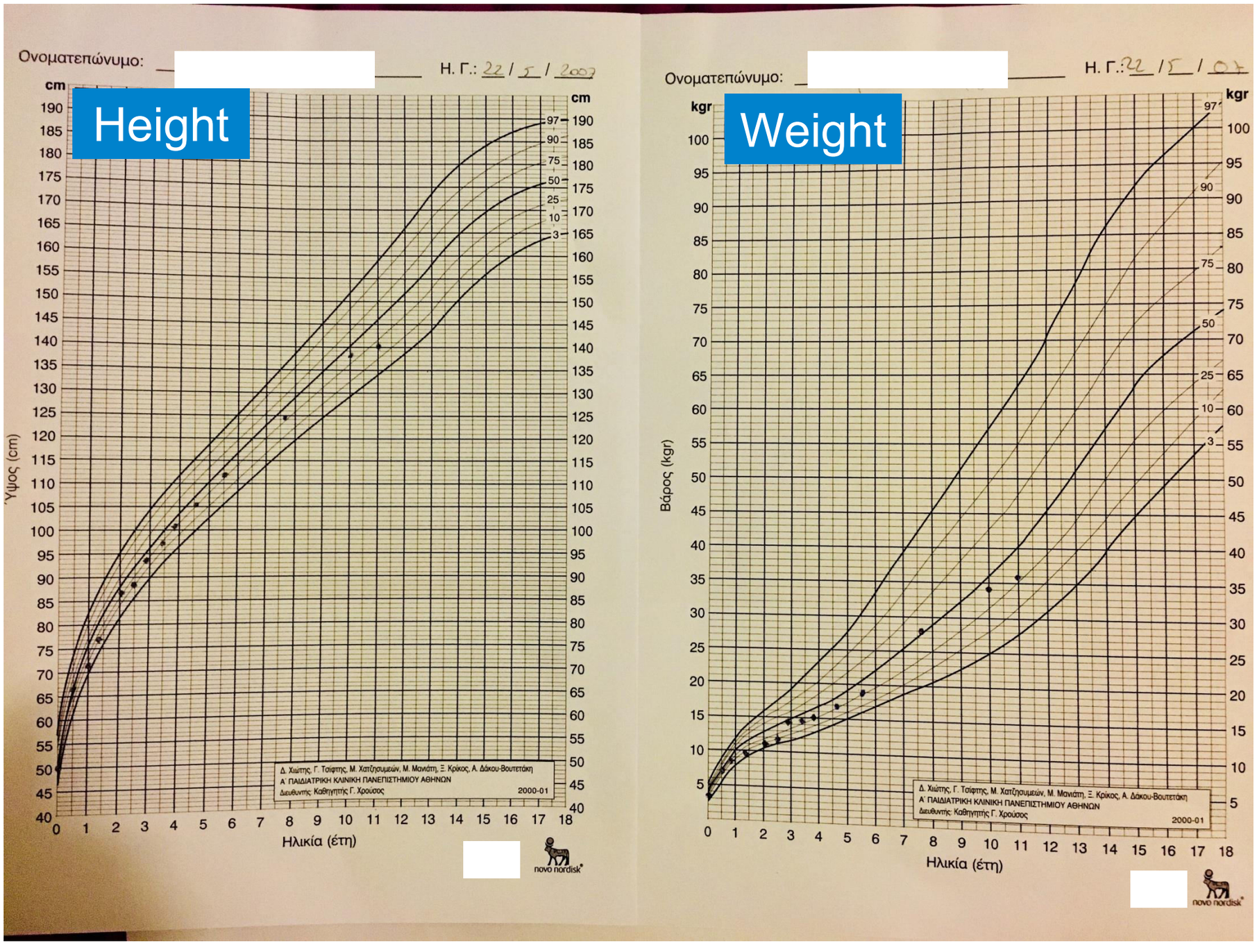
- only few episodes of hypoglycaemia (min. 58 mg/dl) with high Insulin: 25,3 mIU/ml

Patient 3.

The molecular genetic analysis for hyperinsulinism at the Molecular Genetics Laboratory of the University of Exeter Medical School revealed:
a heterozygous missense mutation R269H in the exon 7 of the ***GLUD1*** (glutamate dehydrogenase 1) gene (p.Arg269His) previously reported.
The mutation was not detected in the parents, therefore it was confirmed that it was a *de novo* mutation.

Patient 3.

Growth chart



Patient 3.

- he is now 11 years of age
  body weight: 36 kg (25th p.), height: 140,2 cm (10-25th p.)

- remains eutrophic, normoglycemic and has normal psychomotor development, he also exhibited an adequate anthropometric development under diazoxide treatment

- regularly seen as outpatient in our Division of Paediatric Endocrinology

- last modification of diazoxide treatment: 250 mg/d (6,95 mg/kg/d) divided in 3 doses

Patient 4.

- female newborn,

born at 36 weeks of gestational age to a nondiabetic mother by normal delivery, birth weight: 2540 g

- <u>personal history:</u>

• hypoglycemia detected on the 2nd day of life, 10% glucose infusion rate was required to keep her blood glucose in the normal range. Despite continuous intravenous glucose supplementation and oral feeding, her blood sugar levels still fluctuated up to min 53 mg/dL

• inappropriately normal values of insulin twice detected during episodes with low blood glucose levels (Glu 56 mg/dl with Insulin 2,26 µIU/mL and Glu 63 mg/dl with Insulin 13,04 µIU/mL).

No seizures occurred.

- <u>physical examination: without pathological signs</u>

- hyperinsulinism was suspected, thus initiation of diazoxide therapy at the 43th day of life at a starting dose of 5 mg/kg/d

Patient 4.

The molecular genetic analysis for hyperinsulinism at the Molecular Genetics Laboratory of the University of Exeter Medical School revealed:

a heterozygous missense variant in the exon 6 of the ***GCK*** (glucokinase) gene c.590T>C p.(Met197Thr) previously reported as pathogenic. This result confirmed the diagnosis of autosomal dominant hyperinsulinaemic hypoglycaemia due to an activating *GCK* variant. The mutation was inherited from the father, who was an asymptomatic carrier, while maternal genetic study was normal.

Patient 4.

- she is now 24 months old

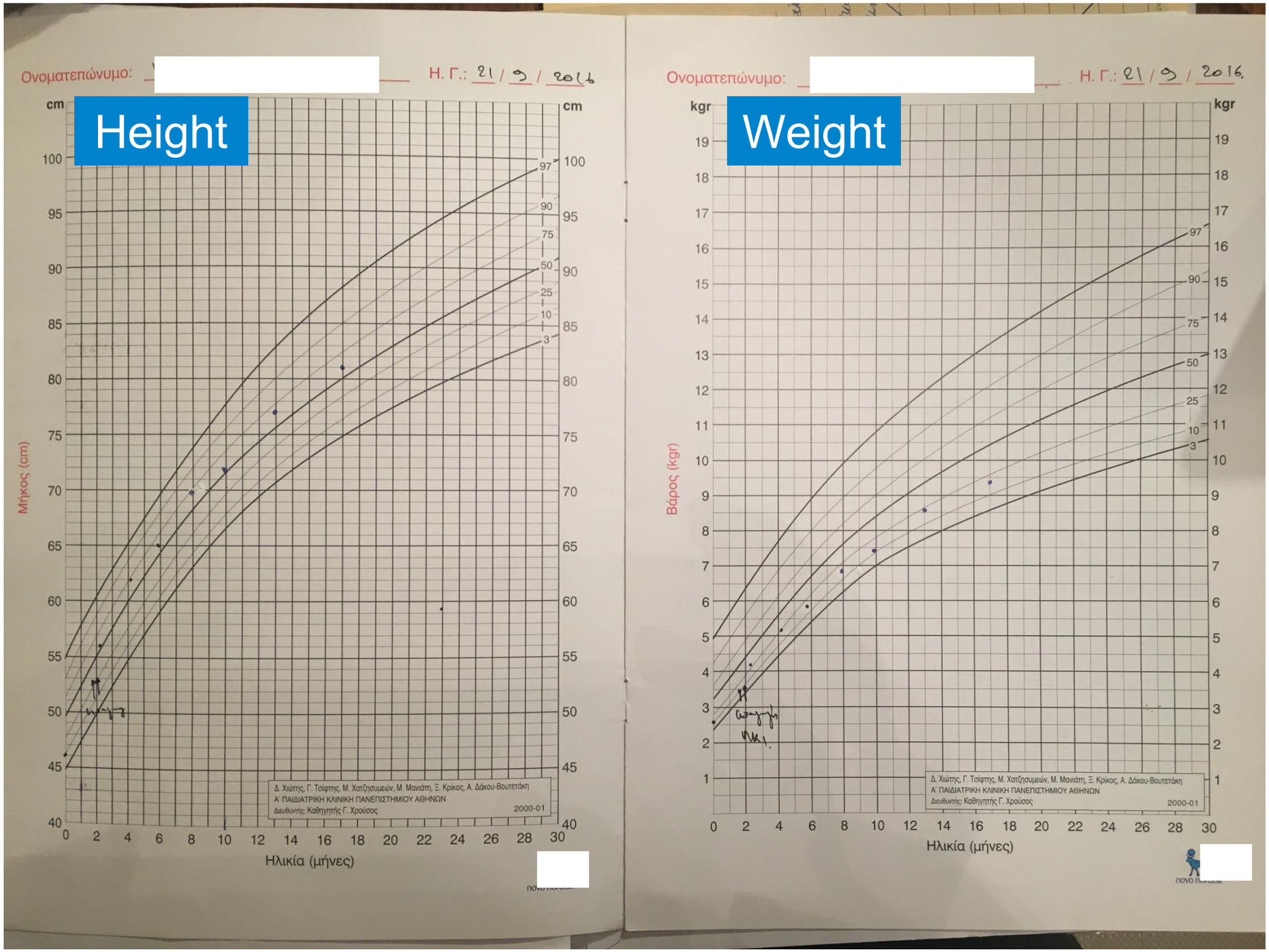
- she remained euglycemic
  progressively reduction of the diazoxide treatment (from 2,3 to 1mg/kg/d) therapy ended at 17 months of age

- she is still being followed up at our outpatient department and has been found to be euglycemic even without diazoxide

- she also has a normal weight and growth development and is fulfilling normal developmental milestones

Patient 4.

Growth chart



Thank you for your attention!