Neonatal diabetes and Glis3 mutation: a new phenotype

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Introduction and objective

The transcription factor Gli-similar 3 (Glis3) is predominantly expressed in the pancreas and it has a critical role in the development of insulin producing β-cells, thyroid and kidney. Mutations in GLIS3 is a rare cause of neonatal diabetes associated with congenital hypothyroidism, congenital glaucoma and polycystic kidney. We report a new case from consanguineous parents with homozygous novel mutation in GLIS3 gene.

Case presentation

M… born to a non-consanguineous couple, was admitted at 15 days of age for hypothyroid

- Antecedents:
  - He was born at 39 weeks of gestation by spontaneous vaginal delivery with a birth weight of 1900 g (<3 percentile), a length of 44 cm (<3 percentile) and a head circumference of 32 cm (10 percentile).
  - Apgar scores= 9/10 ;
  - no maternal history of gestational diabetes or hypertension
  - serology for maternal infection: negative
  - No family history of diabetes mellitus or hypothyroidism
  - Family history of unexplained deaths at low ages (figure 1).

- Clinical examination on admission:
  - Weight = 1800 g
  - temperature: 37°C, heart rate: 140 b/min, blood pressure: 80/40 mmHg
  - he was hypotonic and hypo-reactive
  - archaic reflexes were weak, especially the sucking reflex
  - no abnormalities in his external genitalia

- Laboratory tests:
  - normal blood count (WBC, 12000/mm3, hemoglobin, 15g/dl, platelets, 250 000/mm3); CRP= 2mg/L
  - high blood glucose level : 35mmol/L
  - dipstick urinalysis: glucose 3+, no ketonuria
  - venous blood gas analysis: pH 7.30; pCO2, 8mmHg; pO2, 67mmHg; HCO3 -, 8.3 mmol/L, sodium, 130mmol/L; and potassium, 3.5mmol/L
  - Cerebral fluid, blood and urine cultures were negative for bacteria
  - TORCH screen was negative
  - Plasma C-Peptide level was at 0.43 µg/l (normal 2-9 µg/L)
  - insulin level was high at 44.8 mU/L
  - Blood autoantibody testing against insulin, tyrosine phosphatase-related islet antigen2 (IA2), and glutamic acid decarboxylase (GAD) were negative

- Abdominal ultrasound: structurally normal pancreas and kidneys
- Treatment:
  - subcutaneous protocol of insulin therapy: twice-daily administration of one unit of NPH insulin (Insulatard HM)
  - the diet was divided into eight 60-mL bottles of preterm infant formula in addition to breastfeeding
- At 25 days of life:
  - hypothyroidism was suspected: macroglossia and edema
  - thyroid stimulating hormone (TSH) level in plasma was high (46 µIU/L (normal 0.27–4.2)), thyroid (FT4) level was low (1.2 pmol/L (normal 12–22))
  - Anti-thyroglobulin and anti-microsome antibodies were negative
  - Thyroid anatomy was normal on ultrasound and radioiodine scans
  - Maternal thyroid functions were normal
  - He was initially managed by oral Thyroxin 10 mcg/kg per day

- Evolution:
  - dysmorphic features (microcephaly, flat face, hypotelorism, short nose, smooth and long philtrum, thin upper lip and lower lip vermillion, retrognathia, macrotia with low-set and posteriorly rotated ears, underdeveloped superior crus of antihelix, convergent strabismus (Figure 2,3)
  - psychomotor retardation
  - Ophthalmic examination: bilateral severe glaucoma requiring goniotomy and trabeculectomy
  - Cerebral computed tomography was normal, but the auditory evoked response revealed bilateral endocochlear deafness
  - Skeletal survey showed no skeletal abnormalities
  - liver investigations were normal
  - Abdominal ultrasound: normal liver size and echogenicity, normal kidneys morphology
  - Karyotyping showed 46XY

- Genetic DNA testing for neonatal diabetes: homozygous novel stop mutation in GLIS3 gene (C1597 c A/p S 295 x)

- At different controls:
  - target blood glucose levels difficult to achieve (labile glucose level)
  - current daily dose of insulin: 0.4 IU/kg/day
  - Glycosylated hemoglobin: between 8 and 12%
  - At 17 years and 3 months of age, M…had achieved his puberty (TANNER score = P5 G5) and had a growth delay (weight = 44Kg (-2.5 SD), height = 160cm (-2 SD) and a mild mental retardation

Conclusion

This case is characterized by the absence of renal and hepatic involvement and a particular clinical phenotype with psychomotor retardation and epilepsy