Neonatal diabetes and Glis3 mutation: a new phenotype

Thouraya Kammoun*,Imene Chabchoub*,Kmiha Sana*,Cecile Julier,Mongia Hachicha***

*** Pediatric department, Hedi Chaker University hospital of Sfax,Tunisia**

**** Pasteur Institute, Paris, France**

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 hypotrophy

❖ **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)

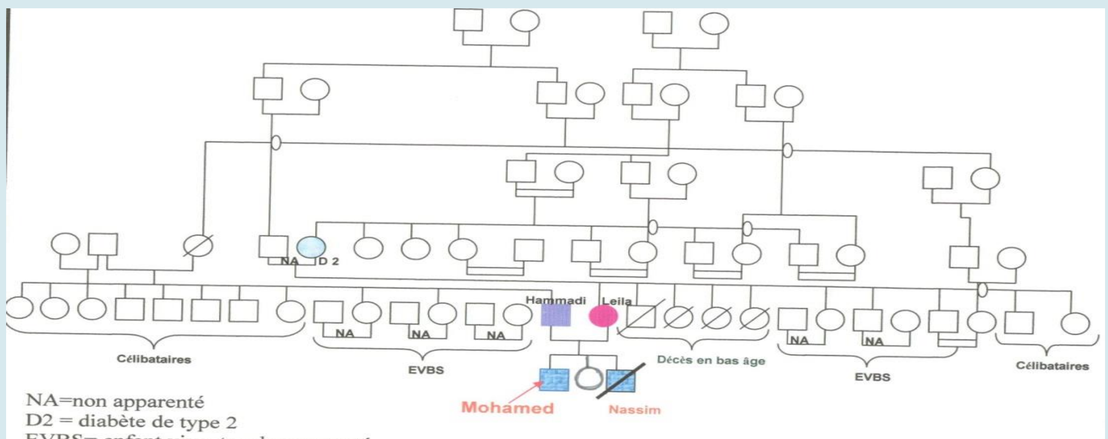


Figure1: Genealogical tree

❖ **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
- TORSCH screen was negative
- Plasma **C-Peptide level** was at **0.43 µg/l** (normal 2-9 µg/L)
- **Insulinemia 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:**

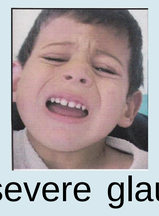
- subcutaneous protocol of insulin therapy: twice-daily administration of one unit of NPH insulin (Insulatard HM)
- the diet was divided into eight 60-mL bottles of preterm infant formula in addition to breastfeeding

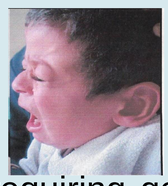
❖ **At 25 days of life:**

- hypothyroidism was suspected: macroglossia and edema
- thyroid stimulating hormone (TSH) level in plasma was high (46 µUI/L (normal 0.27–4.2)), thyroxin (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 vermilion, retrognathia, macrotia with low-set and posteriorly rotated ears, underdeveloped superior crus of antihelix, convergent strabismus (Figure 2,3)



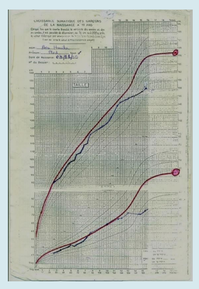


- psychomotor retardation
- Ophthalmic examination: bilateral severe glaucoma requiring goniotomy and trabeculotomy
- Cerebral computed tomography was normal, but the auditory evoked response revealed bilateral endocochlear deafness
- Skeletal survey showed no skeletal abnormalities
- liver investigations 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 (C1597c A/p S 295 x)**

❖ **At different controls**:

- target blood glucoses 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