NEONATAL DIABETES IN TWO SIBLINGS WITH FOXP3 VARIANT

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**Background:** Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is a rare disorder caused by loss-of-function mutations in the gene encoding the forkhead box P3 (FOXP3) transcription factor. This factor plays a key role in the differentiation and function of CD4+ CD25+ natural regulatory T cells, which are essential for the establishment and maintenance of natural tolerance.

**Objective:** To describe clinical, biochemical and genetic characteristics in two siblings with neonatal diabetes and a novel FOXP3 variant.

**Method:** Genomic DNAs were extracted from peripheral blood leukocytes from both patients and their parents with informed consent for genetic studies. Sanger sequencing was performed.

**Results Patient 1:**
- Male, born at term, birth weight 3,050 kg.
- Neonatal diabetes. DKA at 1 month old.
- Glycemia 5,11 g/L. HbA1c 4%. C-peptide 0,1 ng/mL. Anti-insulin Antibodies 13,4 U/mL. Ig E 7710 IU/mL.
- Treatment: NPH and aspartic. Variable glycemic control.
- Severe enteropathy was confirmed by endoscopy and biopsy. Parenteral nutrition. IPEX syndrome was suspected based on neonatal diabetes, enteropathy and eczema.
- Multiple infectious diseases associated with autoimmune cytopenias.
- Died cachectic at 6 months old because of sepsis after 5 months at hospital.
- Sequence analysis confirmed he was hemizygous for a novel FOXP3 frameshift variant resulting in loss of the stop codon, p.(Thr428fs). Evidence up to that moment suggested that the variant was likely pathogenic, consistent with IPEX syndrome. His mother is heterozygous for the mentioned variant, being a carrier.

**Results Patient 2:**
- Male, born at term, birth weight 1,720 kg.
- Neonatal diabetes. Given his older brother record, patient 2’s glycemia was controlled since birth.
- Glycemia 2,5 g/L on first day of life. HbA1c 4%. C-peptide 0,1 ng/mL. GADA 11,1 U/mL. Ig E 2,3 IU/mL.
- Treatment: lispro administered by insulin pump. Variable glycemic control.
- Hydrolyzed formula since birth, hospital discharge at 43 days of life. No persistent enteral symptoms.
- Adequate weight gain.
- His genetic testing showed patient 1’s same variant.
- He successfully received bone marrow transplant at 3 months old.

**Conclusion:** Distinctive manifestations have been described in two siblings with neonatal diabetes as first diagnosis with a novel variant in FOXP3’s Sanger sequence. Their mother is the carrier of the X-linked mutation.

**References:**