A UNIQUE IL2RA MUTATION PRESENTING AS NEONATAL DIABETES, CONGENITAL HYPOTHYROIDISM AND SEPSIS

V. Sri Nagesh1, Andrew Hattersley2, Sian Ellard2, Elisa De Franco2, Sarah Flanagan2, Altaf Naseem3, Ahmed Khan3 ,Tanveer Ahmed3
1. Consultant Endocrinologist, Care Hospital, Hyderabad 2. University of Exeter - Medical School 3. Candy Children's Hospital, Hyderabad

Introduction: To evaluate the neonate for a common cause of neonatal diabetes, congenital hypothyroidism and sepsis and to explore for the best modality of management, including a possible role for sulphonylureas .

Case Presentation

- First child, born of 3rd degree consanguineous marriage.
- Birth and early neonatal period uneventful
- Presented on Day 16 of life with refusal of feeds, excessive crying, fever, dehydration and rapid breathing.
- On examination was febrile with a Heart Rate of 120 per minute, respiratory rate 80 per minute, Oxygen Saturation of 80% and low pulse volume

Investigations	Result
ABG	6.8
SODIUM	147 meq/lt
POTASSIUM	5.5 meq/lt
SERUM CREATININE	1.7 mg/dl
C-REACTIVE PROTEIN	Negative
BLOOD CULTURE	Negative
RBS	22 mmol/lt (400 mg/dl)
HBA1C	10%
T4	0.3 mcg/dl
TSH	>150 mciu/ml

- Diagnosed as DKA and started on insulin drip and iv fluids and 25 mcg thyroxine.
- After resolution of ketosis started on Inj Aspart 30/70 , 2 units morning and 1 unit at night prior to breast feeds.
- This resulted in persistent hypoglycemia and insulin dose was gradually reduced and eventually changed to Glargine 1 unit at bedtime.
- Since hypoglycemia persisted, the dose was reduced to 0.5 unit Glargine and eventually stopped.
- The Blood Glucose shot up to 23 mmol/lt within 2 hours and Glargine was restarted and titrated to 0.2 units in morning and 0.1 unit at night.
- Repeat TSH was > 150 mciu/ml after 15 days.
- Parents confirmed compliance and so dose was increased to 50 mcg/day
- Ultrasound neck – Normal position, size and echotexture of thyroid.

- Diagnosed as Neonatal Diabetes - GLIS3 mutation?
- Sanger sequencing negative for GLIS 3.
- Genetic evaluation for other genes ongoing.

- Readmitted on Day 52 with fever and loose stools.
- Oral thrush, sclerema and abdominal distension.
- CRP – 10 mg/lt.
- S.Creat – 1.5 mg/dl
- Blood culture- sterile
- Started on iv antibiotics, antifungals, albumin and FFP.
- Gradually developed respiratory distress and sclerema
- Bilateral lung crepts and neurological status was dull
- Started on infusions of dopamine, adrenaline and insulin

along with mechanical ventilation and thyroxine was continued.

Investigations	Result
ABG	6.8
CHEST X-RAY	Left upper zone consolidation
POTASSIUM	2.6 meq/lt
SERUM CREATININE	1.5 mg/dl
C-REACTIVE PROTEIN	75 MG/LY
BLOOD CULTURE	Negative
2D ECHO	Moderate to severe LV Dysfunction ? Secondary to sepsis
HBA1C	6.4%
T4	0.3 mcg/dl
TSH	>150 mciu/ml

Developed severe metabolic acidosis and gradually deteriorated
Eventually had refractory hypoxemia and shock and expired.

Targeted Next-Gen Sequencing of neonatal diabetes was ongoing.
Identified a homozygous deletion of exons 2-8 of IL2RA gene.
(IL2RA partial gene deletion, c.65-?_819+?del.)
Both parents heterozygous.
Risk of transmission to next child – 1 in 4.

DISCUSSION

- Immunodeficiency 41 with lympho-proliferation and autoimmunity; IMD 41.Also called CD 25 deficiency.
- An autosomal recessive complex disorder of immune dysregulation.
- Affected individuals present in infancy with recurrent viral, fungal, and bacterial infections, lymphadenopathy, and variable autoimmune features, such as autoimmune enteropathy and eczematous skin lesions.
- Immunologic studies show a defect in T-cell regulation.

- ***Only other case reported worldwide with neonatal diabetes.***

- 8-year-old boy presented at age 6 weeks with diarrhea, insulin-dependent diabetes mellitus, and respiratory insufficiency due to CMV infection.
- During childhood, he developed autoimmune enteropathy with villous atrophy, eczema, lymphadenopathy, hepatosplenomegaly, hypothyroidism, autoimmune hemolytic anemia, and autoimmune granulocytopenia.
- Identified compound heterozygous truncating mutations in the IL2RA gene. Each unaffected parent was heterozygous for 1 of the mutation
- Defective IL-10 expression from CD4 lymphocytes ? Secondary to IL2 receptor mutation.
- Rescued with IL-15 and high concentrations of IL-2.

Survival is difficult in view of recurrent severe infections and extremely limited availability of IL-15 and IL-2.

REFERENCES

P Dimitri et al. Novel GLIS3 mutations demonstrate an extended multisystem phenotype. European Journal of Endocrinology (2011) 164 437–443.

Lowe, C. E., Cooper, J. D., Brusko, T., Walker, N. M., Smyth, D. J., Bailey, R., Bourget, K., Plagnol, V., Field, S., Atkinson, M., Clayton, D. G., Wicker, L. S., Todd, J. A. Large-scale genetic fine mapping and genotype-phenotype associations implicate polymorphism in the IL2RA region in type 1 diabetes. Nature Genet. 39: 1074-1082, 2007.

Vella, A., Cooper, J. D., Lowe, C. E., Walker, N., Nutland, S., Widmer, B., Jones, R., Ring, S. M., McArdle, W., Pembrey, M. E., Strachan, D. P., Dunger, D. B., Twells, R. C. J., Clayton, D. G., Todd, J. A. Localization of a type 1 diabetes locus in the IL2RA/CD25 region by use of tag single-nucleotide polymorphisms. Am. J. Hum. Genet. 76: 773-779, 2005.

Caudy, A. A., Reddy, S. T., Chatila, T., Atkinson, J. P., Verbsky, J. W. CD25 deficiency causes an immune dysregulation, polyendocrinopathy, enteropathy, X-linked-like syndrome, and defective IL-10 expression from CD4 lymphocytes. J. Allergy Clin. Immun. 119: 482-487, 2007.

55ESPE 584--P2
Perinatal Endocrinology
V. SRI
DOI: 10.3252/pso.eu.55ESPE.2016
Poster presented at: ESPE 2016 PARIS