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

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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.

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABG</td>
<td>6.8</td>
</tr>
<tr>
<td>SODIUM</td>
<td>147 meq/lLt</td>
</tr>
<tr>
<td>POTASSIUM</td>
<td>5.5 meq/lLt</td>
</tr>
<tr>
<td>SERUM CREATININE</td>
<td>1.7 mg/dl</td>
</tr>
<tr>
<td>C-REACTIVE PROTEIN</td>
<td>Negative</td>
</tr>
<tr>
<td>BLOOD CULTURE</td>
<td>Negative</td>
</tr>
<tr>
<td>RBS</td>
<td>22 mmol/lLt (400 mg/dl)</td>
</tr>
<tr>
<td>HBA1C</td>
<td>10%</td>
</tr>
<tr>
<td>T4</td>
<td>0.3 mcg/dl</td>
</tr>
<tr>
<td>TSH</td>
<td>&gt;150 mcIU/ml</td>
</tr>
</tbody>
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• Diagnosed as DKA and started on insulin drip and IV fluids and 25 mcg thyroxine.
• After resolution of ketosis started on Ins 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/lLt 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/lLt.
• 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 crests and neurological status was dull.
• Started on infusions of dopamine, adrenaline and insulin along with mechanical ventilation and thyroxine was continued.

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 homozgyous deletion of exons 2-8 of IL2RA gene. (IL2RA partial gene deletion, c.657_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 autoimune 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


