NEONATAL DIABETES ON GLIBENCLAMIDE THERAPY

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Diabetic clinic
ICH&HC
82 days old male infant

Breathlessness and poor feeding x 2 days

H/O Polyuria and Frequent feeds since 6 weeks of life

No family history of diabetes
BIRTH HISTORY

First born child of NCM parents

Antenatal and birth history - nothing significant

Delivered as a term baby of 2.4 kg birth weight
Lethargic

No Dysmorphic Features

HR-150/min

RR-70/min, Effortless tachypnea
<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Glucose</td>
<td>450mg/dl</td>
</tr>
<tr>
<td>Blood gases</td>
<td>Severe metabolic acidosis</td>
</tr>
<tr>
<td>Urine analysis</td>
<td>Ketonuria</td>
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</tbody>
</table>
Treated as DKA

Stabilized on twice daily intermediate acting insulin therapy.

Discharged and followed up in the diabetic clinic.

At 6 months -started on twice daily insulin as a combination of short and intermediate acting insulin.
<table>
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<tr>
<td>C peptide levels</td>
<td>0.1pmol/ml (n 0.3 - 1.4 pmol/ml)</td>
</tr>
<tr>
<td>GAD</td>
<td>&lt;6.54 IU/ml (normal&lt;10 IU/ml)</td>
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<tr>
<td>Hba1c level</td>
<td>7.97%</td>
</tr>
<tr>
<td>Insulin antibodies</td>
<td>0.5 IU/ml (normal&lt; 15 IU/ml)</td>
</tr>
<tr>
<td>Lipid profile</td>
<td>Normal</td>
</tr>
<tr>
<td>Thyroid function test</td>
<td>Normal</td>
</tr>
<tr>
<td>Skeletal workup</td>
<td>Normal</td>
</tr>
<tr>
<td>LFT</td>
<td>Normal</td>
</tr>
</tbody>
</table>
HBA1c maintained between 6.9 – 8.9%

Genetic analysis was done at 16 months for $\text{Kir} 6.2, \text{ABCC} 8$. 
Sequencing analysis -
Heterozygous for a missense mutation C42R, in the KCNJ11 gene.

This T>C mutation at nucleotide 124 resulted in the substitution of the aminoacid arginine for cysteine at codon 42.
Father and mother - negative for this mutation.

Diabetes mellitus due to this mutation - found to be responsive to oral sulphonylurea therapy.
Admitted and baseline C peptide and HBA1c levels were taken.

Child was on twice daily combination of **short and intermediate acting insulin** 10 units per day.

**Oral Glibenclamide** tablets were powdered into packs of 0.5 mg each and was started at a dose of 0.05 mg/kg/dose twice daily in increments of 0.1 mg/kg/day up to 1 mg/kg/day.
Simultaneous reduction of insulin done under strict blood glucose monitoring. At the end of six days child was completely off insulin.

Oral glibenclamide was titrated to 0.5mg/kg/day at discharge.

Blood glucose levels-120mg/dl - 150mg/dl during self monitoring at home after discharge.
After 5 months of OHD

- HbA1C-5.18
- C-peptide-0.737ng/ml(0.81-3.85)
Neonatal diabetes mellitus (NDM) is a rare metabolic disorder. Incidence: 1:300,000–400,000 newborns. Characterized by hyperglycemia combined with low levels of insulin. Two types: Transient NDM (TNDM) and Permanent NDM (PNDM).
Transient neonatal diabetes mellitus

**Chromosome 6 anomalies detected**
- paternal duplications
- paternal isodisomy
- Methylation defect

- **ABCC8 (SUR1) and rarely KCNJ11 (Kir6.2) mutations**

Permanent neonatal diabetes mellitus

- Heterozygous activating mutation in *KCNJ11* gene and in *ABCC8* gene (*Kir6.2 and SUR1* subunits of the pancreatic KATP channel)
- **IPEX syndrome**: diffuse autoimmunity
- Mitochondrial disease
- Severe pancreatic hypoplasia associated with IPF1 (*PDX1*) mutation
- Homozygous glucokinase mutation: insensitivity to glucose
- Associated with epiphyseal dysplasia: Wolcott Rallison syndrome
- Possibly associated with enterovirus infection
- Association with cerebellar hypoplasia and *PTF1A* mutation
- Association with hypothyroidism, glaucoma and *GLIS3* mutation
CLINICAL FEATURES:

TNDM is a developmental disorder of insulin production that resolves postnatally.

Incidence - 50% to 60%

Intrauterine growth retardation (IUGR), hyperglycemia, failure to thrive and, in some cases, dehydration occur after birth.

Most patients recover within a year.
less common

diabetes develops in the neonatal period does not go into remission

do not always have IUGR

More likely to develop keto acidosis

other features are similar to TNDM
mechanism

Glucose increase

Low glucose concentration

ATP/MgADP

K^+

Hyperpolarization

-70 mV

Insulin secretion

Ca^{2+}

ATP/MgADP

Ca^{2+}

Depolarization

Channel K^+ (ATP) closed

Normal subject
Heterozygous activating mutations in the *KCNJ11* and *ABCC8* genes encoding the Kir6.2 and SUR1 subunit of the pancreatic beta-cell potassium ATP (KATP) channel cause PNDM. This mutations led to an increase probability of opening of the potassium channel therefore preventing any activation of the voltage dependent calcium channel and any glucose induced insulin secretion.
Infants with diabetes

Confirm the diagnosis, stabilise the patient

Do c-peptide, insulin antibodies, GAD

Plan to do genetic analysis
TREATMENT

Patients with permanent neonatal diabetes due to a *KCNJ11* or a *ABCC8* mutation, transfer from insulin injections to oral glibenclamide therapy is highly effective for most patients and safe.
Treatment changes from Painful multiple daily injections To oral sulfonylurea therapy

Take home message

ALL INFANTS WITH DIABETES SHOULD UNDERGO GENETIC STUDY
Thank you for your patient listening.