Clinical characteristics and molecular analysis of patients with neonatal diabetes

Zehra Yavas Abali¹, Ruveyde Bundak¹, Firdevs Bas¹, Elisa De Franco², Mikayir Genens¹, Sukran Poyrazoglu¹, Sian Ellard², Andrew T Hattersley, Feyza Darendeliler

¹Istanbul University, Istanbul Faculty of Medicine, Pediatric Endocrinology, ²Institute of Biomedical and Clinical Science, University of Exeter Medical School

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Background
Neonatal diabetes mellitus (NDM) is a form monogenic diabetes diagnosed before 6 months of age.

Objective
To describe the clinical and molecular characteristics of NDM patients in a Turkish cohort.

Methods
Fifteen patients (13 M, 2 F) with diabetes onset before 6 months of age were included in the study. Clinical and molecular data were evaluated retrospectively.

Result
Mean age at diagnosis was 2.4±1.5 months (median 2, range 0.5-6 m).
Gestational ages were between 35-40 weeks.
Birth weight (BW) was between 1400-3680g and BW-SDS -1.7±1.7 (median -1.1; range -5.0 – 0.6).
Small for gestational age (SGA, BW <-2 SD) ratio was 40%.
Consanguinity ratio was 66.7%.
Mean serum glucose level at diagnosis was 29.4±8.9mmol/l.
Mutations are given in Table 1.

Table 1. Genotype analyses of the patients

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Patients (n)</th>
<th>Mutations detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCC8</td>
<td>3</td>
<td>p.E382K and p.R826W</td>
</tr>
<tr>
<td>PTF1A</td>
<td>2</td>
<td>g.23508437A&gt;G</td>
</tr>
<tr>
<td>Thiamine responsive</td>
<td>1</td>
<td>p.S214fs in SLC19A2</td>
</tr>
<tr>
<td>megaloblastic anemia</td>
<td></td>
<td>distal enhancer</td>
</tr>
<tr>
<td>Wolcott Rallison</td>
<td>1</td>
<td>p.S718TfsX723 in</td>
</tr>
<tr>
<td>syndrome</td>
<td></td>
<td>EIF2AK3</td>
</tr>
<tr>
<td>INS</td>
<td>1</td>
<td>c.-331C&gt;G</td>
</tr>
<tr>
<td>Not known</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

In two siblings with ABCC8 mutations (p.E382K mutation), insulin therapy was switched to glibenclamide at the age of 15 and 11 years. They have been on sulphonylurea (SU) monotherapy for 9 years, recent HbA1c values were 6.5%.
The third patient with ABCC8 mutation (p.R826W) was planned to transfer SU.
The two patients with PTF1A mutation had exocrine pancreatic deficiency due to pancreatic hypoplasia.
One patient with unknown genetic etiology was SGA and had also exocrine pancreatic deficiency.
Patient with SLC19A2 mutation has sensorineural deafness, megaloblastic anemia, AV block, still on thiamine and subcutaneous insulin therapy (0.8 U/kg/day) at the age of 7 years.
Patients with mutations in INS, PTF1A and two patients with unknown genetic etiology were SGA.
One patient had no mutation in ABCC8 and KCNJ11 gene. Genetic cause was not resulted in six patients.

Conclusion
With high consanguinity ratio in this cohort, Wolcott Rallison syndrome was not the most common cause of NDM, contrary to previous reports.
Male dominancy of our cohort was also noteworthy.
In NDM patients with SGA and exocrine pancreatic deficiency PTF1A should be analysed first.