Clinical details, Molecular genetic analysis AND Clinical phenotype correlation of 14 patients with Neonatal diabetes from the South India – A Single Centre Experience

V, Sri Nagesh1, Andrew Hattersley, Sian Ellard2, Elisa De Franco2, Sarah Flanagan2, Bipin Sethi1, Altaf Naseem3, Syed Tanveer Ahmed4
1. Consultant Endocrinologist, SriNagesh Clinic, Hyderabad 2. University of Exeter - Medical School 3. CARE Hospital, Hyderabad 4. Candy Children’s Hospital, Hyderabad

Background
Neonatal diabetes typically presents within the first 6 months of life. Often misdiagnosed as Type 1 Diabetes and on lifelong insulin therapy. Doctors unaware of monogenic variants. Recent studies report prevalence much higher at 1 in 90,000. NDM prevalence is probably higher in India due to the high frequency of consanguineous marriages, especially in South India. Few studies reported, mostly from South India. No nationwide studies or genotype-phenotype co-relation

AIMS AND OBJECTIVES
• Describe the molecular genetics of a South Indian cohort of NDM patients referred to a single centre
• Correlate the clinical characteristics and follow-up picture to the genotype.
• Attempt transition to Sulphonylurea in children with ABCC8 and KCNJ11 mutations.

Materials & methods
◆ Patients referred with NDM between the period of Nov 2014 to April 2017 were included in the study.
◆ Retrospective analysis and case finding in patients who were assumed to have Type 1 diabetes mellitus and who were under follow-up, when the clinical phenotype was consistent with monogenic diabetes.
◆ Details of clinical presentation, birth and family history, clinical phenotype, biochemical data, imaging and management were collected using a standardised proforma.
◆ Study performed according to the principles of the Declaration of Helsinki with written informed consent given by the patients’ parents for genetic analysis. Telephonic consent was also obtained from the parents prior to compiling information for this paper.

Genetic Analysis
EDTA blood samples of infants and both parents (wherever possible) were sent for molecular genetic analysis. Genomic DNA was extracted, and the coding regions and intron/exon boundaries of the ABCC8, KCNJ11, INS and EIF2AK3 genes amplified by PCR. Amplicons were sequenced using the Big Dye Terminator Cycler Sequencing Kit v3.1 (Applied Biosystems), and reactions were analysed on an ABI 3730 Capillary sequencer (Applied Biosystems).

Sanger sequencing was used to validate the screened mutations and in parents for inherited or de novo mutations.

Confirmed mutations were then searched in the human gene mutation database (HGMD), dbSNP[13], thousand genomes, and recent reviews. For all mutations, software Polyphen-2 was used to predict the pathogenicity.

Statistical analysis was performed using IBM SPSS 22.0 for Windows statistical software. Wherever feasible, data was expressed as mean ± S.D.

CRITERIA
Inclusion Criteria
Age at onset <9 months
Hyperglycemia sustained for ≥ 2 weeks
Insulin dependence

Exclusion Criteria
Exclusion of
Hyperglycemia caused by stress and infection and drug therapies.

Highlights
• One of the larger cohorts described recently.
• Good genotype–phenotype correlation
• Demonstrated DQ improvement with SU therapy
• S novel mutations
• Genetic evaluation was thorough and included a 29 gene panel.
• Tracking of parents and grand parents and screening
• More Permanent vs transient NDM

Limitations
• Antibody testing to rule out T1DM - not financially feasible.
• Could not measure c-peptide prior to and during transition to SU Therapy
• Parents of a few children could not be tested due to various reasons like distance, death, diaspora and divorce.

CONCLUSIONS
• Mutations in GCK, KCNJ11 AND INS were the commonest causes of NDM in our cohort.
• Underlying mutations established in 75%.
• More non-KATP channel mutations are likely to reflect the increased rate of consanguinity.
• In countries with more consanguineous marriages, focused searching for rarer causes of NDM and creation of database needs to be done, so that targeted high yield genetic sequencing can be performed.

REFERENCES