Neonatal Diabetes

Experience from a Single Centre in Sri Lanka

N Atapattu[1], D H de Silva[1], S de Silva[1], M M Jayathilaka[1], S Flanagan[2], Andrew T. Hattersley[2], Sian Ellard[2], J.A.L Houghton[2] , K. Hussain[3]

[1]Lady Ridgeway Hospital for Children, Colombo, Sri Lanka, [2]Molecular Genetics, Royal Devon & Exeter Hospital, Barrack Road, Exeter, UK , [3]UCL Institute of Child Health Great Ormond Street Hospital for Children, UK

Introduction

- Neonatal diabetes (NDM) is defined as hyperglycemia within the first few months of life, lasting more than 2 weeks(1).
- NDM is a rare form of diabetes (1:300 000-1:400 000)
- wo main groups have been identified based on clinical grounds, the duration of treatment (Transient, Permanent)
- Transient neonatal diabetes mellitus (TNDM) accounts for 50-60% of all NDM, which develops within first few weeks of life and usually go in to remission in few months
- >50 % of patients with TNDM are associated with abnormalities of an imprinted region on chromosome 6q24 (2)
- Defects in KCNJ11, ABCC8, INS, GCK, PDX1 genes lead to permeant neonatal diabetes PNDM
- Heterozygous activating mutations in the KCNJ11 gene results in 33 -50% of cases of PNDM
- Defects in PTF1A, FOXP3, EIF2AK3, GLIS3, RFX6, and NEUROD1 genes are very rare and may lead neonatal diabetes as a part of a syndrome
- No clinical features predict which patient end up having PNDM
- Molecular diagnostic tests lead to unexpected change in treatment options
- Patients with KCNJ11, ABCC8 can successfully be transferred from insulin therapy to sulfonylurea

Objective

- To describe the clinical characteristics and molecular genetics of a cohort of patients with NDM presented to Lady Ridgeway Hospital

Method

- All patients referred to Lady Ridgeway Hospital (LRH) from August 2013 to February 2015 with neonatal diabetes who had molecular genetic analysis were included
- Ethical approval was obtained from LRH
- Age of presentation, birth weight ,sex, associated clinical features were obtained from database
- Tests were done in the Institute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter, UK

Results

- 10 patients (7 male) diagnosed neonatal diabetes
- All patients had ketoacidosis at presentation
- Sequence analysis identified mutations in 9 of the 10 patients (90%) screened
- One patient had a mutation associated with transient NDM but did not go in to remission
- Consanguinity was reported in one family

Four patients were heterozygous for a K-ATP channel mutation (40%)

Age at diagnosis (Birth weight)	sex	Mutation	Response to sulfonylurea	Parents	Associated features	Follow up (HbA1c)
6 months (2.7kg)	Male	heterozygous KCNJ11 missense mutation, p.V59M	yes	Mother unaffected	Development delay, Short stature, learning disability	Expect to improve cognitive function , muscle tone (7.6%)
2 months (2.5kg)	Male	heterozygous KCNJ11 missense mutation, p.R50Q	yes	Parents not affected	no	(8%)
8months (2.4kg)	Female	heterozygous ABCC8 missense mutation, p.E208K	yes	Mother same mutation	No	Relapse and remission. Mother has a risk of diabetes (5.6%)
2months (2.1kg)	Female	KCNJ11 heterozygous missense mutation, p.R50P	No	unaffected	Development delay	Epilepsy

2 patients had *INS* mutation (20%)

Age at diagnosis (Birth weight)	sex	mutation	Parents/sibling	Associated features	Follow up (HbA1c)
4 months (2.7kg)	male	heterozygous INS Mutation (p.R89C)	unaffected	No	Good response to insulin(8.2%)
2 months (2.94kg)	male	heterozygous INS mutation (p.R89C)	unaffected	No	Good response to insulin(7.8%)

2 patients had *EIF2AK3* mutation

Age at diagnosis	sex	mutation	Associated features	Parents	Follow up (HbA1c)
2 months (3.2kg)	Male	Homozygous missense mutation, p.S991N, in EIF2AK3	Atlanto axial subluxation, skeletal dysplasia, liver failure	Parents heterozygous	Renal failure, Learning disability, neutropenia, recurrent infections, osteopenia (7.8%)
2 months (2.7kg)	female	homozygous nonsense mutation, (p.L863, in EIF2AK3	Atlanto axial subluxation, skeletal dysplasia, liver failure	Mother h eterozygous	

1 patient *FOXP3* mutation

Age at diagnosis	sex	mutation	Parents	Associated features	Follow up (HbA1c)
9 months (3kg)	Male	novel hemizygous missense mutation, p.E412D.	Mother heterozygous	Nephrotic	Immune dysregulation, polyendocrinopathy Enteropathy, dermatitis (7.2%)

Conclusion

- KCNJ11 mutation was the commonest reason for NDM
- Molecular diagnostic tests of NDM help to provide genetic counselling for parents
- Determine treatment modalities
- Anticipate potential complications

References

1. Sperling M A: Neonatal Diabetes Mellitus: from understudy to centre stage. Curr Opin Pediatr 2005; 17 : 512—518
2. Metz C, Cave H, Bertrand AM, et al. Neonatal diabetes mellitus: chromosomal analysis in transient and permanent cases. J Pediatr 2002;141:483-9.

ESPE 2015 278--P2

Diabetes and Insulin

Navoda Atapattu

DOI: 10.3252/pso.eu.54espe.2015

Poster presented at: ESPE 2015 BARCELONA