Empirical sulphonylurea in Neonatal diabetes: results from a Tertiary care center.

Smita Ramachandran, Inderpal Singh Kochar. Indraprastha Apollo Hospital New Delhi, India.

Introduction

Neonatal diabetes (NDM) is a rare condition presenting wit hyperglycemia within the first 6 months of life. It can be transient (TND) or permanent (PND) and are usually associated with genetic defects [1].

NDM occurs in approximately in 90,000-1,60,000 live births and over 20 mutations have been identified [2].

TND constitute about 50-60% of all NDM and tens to resolve by 12weeks, but may recur later, during periods of increased insulin resistance namely puberty and pregnancy [3].

In this study we attempted to evaluate the risk and benefits of starting glibenclamide with insulin in neonatal diabetes before the results of genetic testing.

Study Design

Subjects:

- The hospital records of patients aged <6 months at diagnosis of NDM were reviewed retrospectively.
- The children were admitted in the Pediatric Endocrinology department of Indrapastha Apollo hospital.Neonatal diabetes was diagnosed in children less than 6 months of age at presentation, polyuria, dehydration, failure to gain weight, random blood sugar >200mg/dl.

Methods:

- All the infants were admitted and started on subcutaneous insulin detemir, starting at a dose of 0.3U/kg/day and 2-3 doses of insulin lispro were given, titrated according to the blood sugars
- Genetic mutation analysis was done after obtaining informed consent from the parents
- All the infants has Sanger sequencing done for the KCNJ11, ABCC8 and INS genes and expanded sequencing was done in one case with FOXP3 mutation.

Empirical glibenclamide was given only in infants with the following criteria:
requiring high doses of insulin > 0.7U/kg/day and
persisting hyperglycemia
with no associated diarrhea, syndromic features, dermatits
non consanguineous parents
A trial of oral glibenclamide starting at 0.2mg/kd/day along with the subcutaneous insulin.
Four infants fulfilling these criteria were given a trial of glibenclamide

Results

- 4 infants (case 1, 2, 7,11) were given a trial of empirical glibenclamide after sending the samples for genetic testing. All these infants were receiving insulin at a dose of >0.8U/k/d, and were not euglycemic on this dose, none of the parents of these cases had consanguineous marriage, and had no syndromic features.
- Three of the cases (2,7,11) responded favorably and insulin was tapered off slowly.
- However in case no 1, there was an initial reduction on insulin dose and we were able to stop insulin, but within a month the child became hyperglycemic and was restarted on insulin.
- Even in the single case no 1, in which glibenclamide was not successful, there were no side effects to it.

References:

1.Naylor, R. N., S. A. W. Greeley, G. I. Bell, and L. H. Philipson. 2011. Genetics and pathophysiology of neonatal diabetes mellitus. J. Diabetes Investig. 2:158–169.
2.Letourneau LR, Carmody D, Wroblewski K, et al. Diabetes presentation in in- fancy: high risk of diabetic ketoacidosis. Diabetes Care 2017;40:e147–8.
3.Aguilar-Bryan L, Bryan J. Neonatal diabetes mellitus. Endocr Rev. 2008;29(3):265–291.

Results

Table: 1. Clinical features at presentation in patients with a diagnosis of NDM

	S.no	Gene	Location	Mutation	Mutation DNA level	Zygosity	Sex	Treatment	Age at presentation	Diagnosis
	1	FOXP3	Exon 10	missense	c.1040 G>A	Hemizygous	M	Insulin 1u/k/d Glibenclamide 0.3mg/k/d	25 days	IPEX syndrome
	2	KCJN11	Exon 1	missense	c.685 G>A	Heterozygous	M	Glibenclamide 0.4mg/k/d	4mths	TND
	3	HNF1B	Novel	missense	p.S19C	Heterozygous	M	Insulin 0.4u/kg/d	4mths	PND
	4	No mutation detected	-	-	-	-	M	Insulin 0.4u/k/d	3mths	TND
	5	EIF2AK3	Exon 5,13	frameshift	c.287 G>A,/ c.2511_2514del	Heterozygous	F	Insulin 0.8u/k/d	1.2 mths	Wolcott Rallison syndrome
	6	INS	Exon 3	missense	c.287 G>A	Heterozygous	F	Insulin 0.7u/k/d	3mths	PND
	7	No mutaion detected	-	-	-	-	F	Insulin 0.8u/k/d glibenclamide 0.4mg/kg/d	1.2 mths	TND
	8	No mutaion detected	-	-	-	-	M	Insulin 0.5u/k/d	4 mths	TND
	9	No mutaion detected	-	-	-	-	M	Insulin 0.3u/k/d	3 mths	TND
	10	No mutation detected	-	-	-	-	M	Insulin 0.4u/k/d	3 mths	TND
	11	KCJN11		p.R201H		Heterozygous	F	Glibenclamide 1mg/k/d	4 mths	PND 11

Conclusion

- This study reiterates the need to genetically test all cases of NDM, but a trial of sulphonylurea can be attempted in certain cases, but only in supervised tertiary care centers under endocrinology guidance.
- There were no adverse events on the children treated empirically, even in the case where glibenclamide was unsuccessful.
- Larger studies with longer follow-ups are needed to evaluate the entire spectrum of the outcomes.

Conflict of Interest: The authors have no real or perceived conflicts of interest in any matters, including financial issues, relating to this work.