DIAZOXIDE RESPONSIVE CONGENITAL HYPERINSULINISM

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BACKGROUND

- Congenital Hyperinsulism (CHI) is a common cause of recurrent and persistent hypoglycemia in the neonatal period. (1)
- Diazoxide is an FDA approved drug used in treating CHI. (2)
- It activates sulfonylurea receptor of ATP-sensitive potassium (KATP) channel on β-cell of pancreas leading to suppression of insulin secretion. It is widely used in management of CHI. (3, 4)

AIM

- To report the clinical, laboratory, treatment and outcome profile of diazoxide responsive CHI from a tertiary pediatric endocrine unit

METHOD

- A retrospective study at a tertiary pediatric endocrine unit (from January 2012 to Nov 2019).
- Inclusion criteria- children diagnosed with CHI during the episode of hypoglycemia, elevated c peptide level inappropriately suppressed ketones and free fatty acids who were responsive to diazoxide
- Children switched to octreotide or lost to follow-up or transferred to other centers were excluded.
- Out of 103 children who were diazoxide responsive 13 were excluded from the study and data of 90 children was included and analysed.
- Detailed history, clinical findings, biochemical parameters, 2 D-echocardiography, adverse events following diazoxide therapy, genetic analysis & long-term follow-up data were noted.
- All data were entered in MS excel 2016.
- Analysis was performed with SPSS v 21.
- P <0.05 was considered significant.

RESULTS

- Among 90 children (males= 69.4%) 72 were diagnosed in neonatal period.
- Only in 18.1% children diazoxide therapy was required for >2 yrs
- On comparison of those required treatment of <2yrs & >2yrs it was noticed that c-peptide level were significantly high in children requiring longer duration therapy.
- Among those requiring therapy for > 2yrs, 23.1% were genetically positive as compared to 5.1% among those needing treatment <2 years.

Gene	Type of Mutation	Treatment (in yrs)	Follow-up status
11p15 methylation defect	1	0.61	Off treatment
HNF4A	heterozygous – 1 compound heterozygous- 1	4.5 years 4.3 years	Both on treatment
HNF1A	1	5.6 years	On treatment
INSR	1	1.4 years	Off treatment
GLUD1	1	9.3	Off treatment
ABCC8	Heterozygous missense-1 Homozygous- 3	1.03 yrs (1.9 yrs, 0.9 yrs, 0.3 yrs)	3 On & 1 off treatment

Table 4. Positive Genetic mutation description of the study population

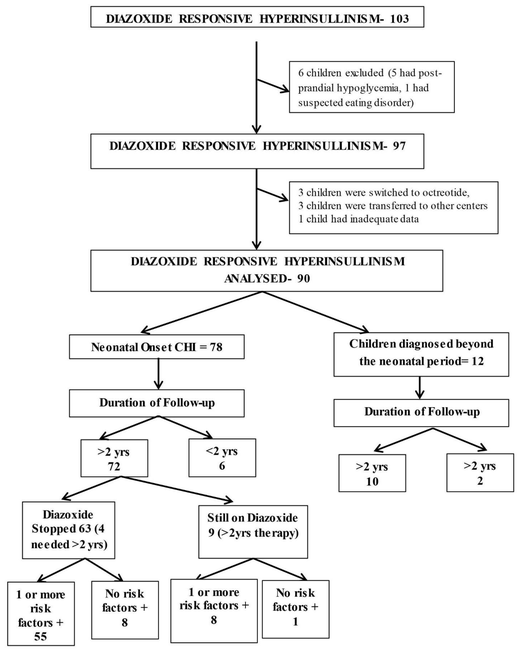

Fig 1. Description of study population of diazoxide responsive CHI

	N (%)
T1DM in mother	2 (2.8%)
GDM	7 (9.7%)
Beta Blockers use (PIH)	3 (4.2%)
Twin Pregnancy	7 (9.7%)
IUGR/SGA	26 (36.1%)
LGA	12 (16.7%)
Perinatal Distress	10 (13.9%)
Preterm Birth	24 (33.3%)
Children requiring therapy <2 yrs	59 (81.9%)
Children requiring therapy > 2yrs	13 (18.1%)
Off Therapy	63 (87.5%)
Ketotic Hypoglycemia	7 (9.7%)

Table 1 Profile of diazoxide responsive neonatal CHI (categorical variable)

	Range	Mean	SE Mean
Age at diagnosis (Day of life)	0-25	1.36	0.425
BW SDS	-3.51- 3.21	-0.46	0.24
Blood Glucose (mmol/L)	0.2-2.8	1.88	0.06
Insulin (pmol/L)	18.5-1357	149.5	28.78
C- peptide (pmol/L)	169-3280	733.46	80.7
Peak GIR (mg/kg/min)	8-33	14.7	28.8
Diazoxide initiating dose (mg/kg/day)	1-10	3.46	0.18
Diazoxide at optimum response (mg/kg/day)	1-10	4.04	0.22
Chlorothiazide (mg/kg/day)	3-10	6.39	0.3
Duration of therapy (Yrs)	0.0082-7.8	1.48	0.22

Table 2. Profile of diazoxide responsive neonatal CHI (continous variable)

	< 2 years Therapy (N=59)			> 2 years Therapy (N=13)			
	Mean	SEM	Range	Mean	SEM	Range	P
Age at Diagnosis (day of life)	0.76	0.19	0-7	4.1	2.1	0-25	0.1
Birth Weight (SDS)	-0.54	0.24	-3.50- 2.9	-0.06	0.72	-3.42- 3.2	0.47
Blood glucose (mmol/L)	1.9	0.07	0.8- 2.8	1.6	0.24	0.2- 2.5	0.24
Insulin (pmol/L)	118.9	21.7	18- 1100	308.5	132.8	24- 1357	0.59
C peptide (pmol/L)	607.9	59.3	169- 2022	1224.5	285.7	292- 3280	**0.02**
Peak GIR (mg/kg/min)	14.3	0.8	8- 33	17	1.8	12- 25	0.21
Initial dose of diazoxide	3.5	0.2	1-10	3.3	0.2	2- 5	0.75
Responsive Dose	3.95	0.24	1-10	4.5	0.6	2- 10	0.38

Table 3. Comparison of <2 years and > 2years group

CONCLUSIONS

- We have reported children with diazoxide responsive CHI where the median duration of therapy is shorter in neonatal onset CHI compared to those with late onset.
- Also most of the neonatal onset CHI had risk factors present and diazoxide was eventually discontinued in majority of them.
- Genetics were negative in majority of the diazoxide responsive patients who had transient CHI.

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