Phenotype, Genotype and Short term Outcome in Congenital Hyperinsulinism(CHI)

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Introduction

Congenital hyperinsulinism (CHI) is the commonest cause of intractable hypoglycaemia in neonates and infants. Hyperinsulinemic hypoglycaemia occurs due to unregulated insulin secretion from β-cells of pancreas in relation to blood glucose levels*.

Aim

- To describe clinical profile , molecular characterization , response to therapy and short term outcome in CHI.

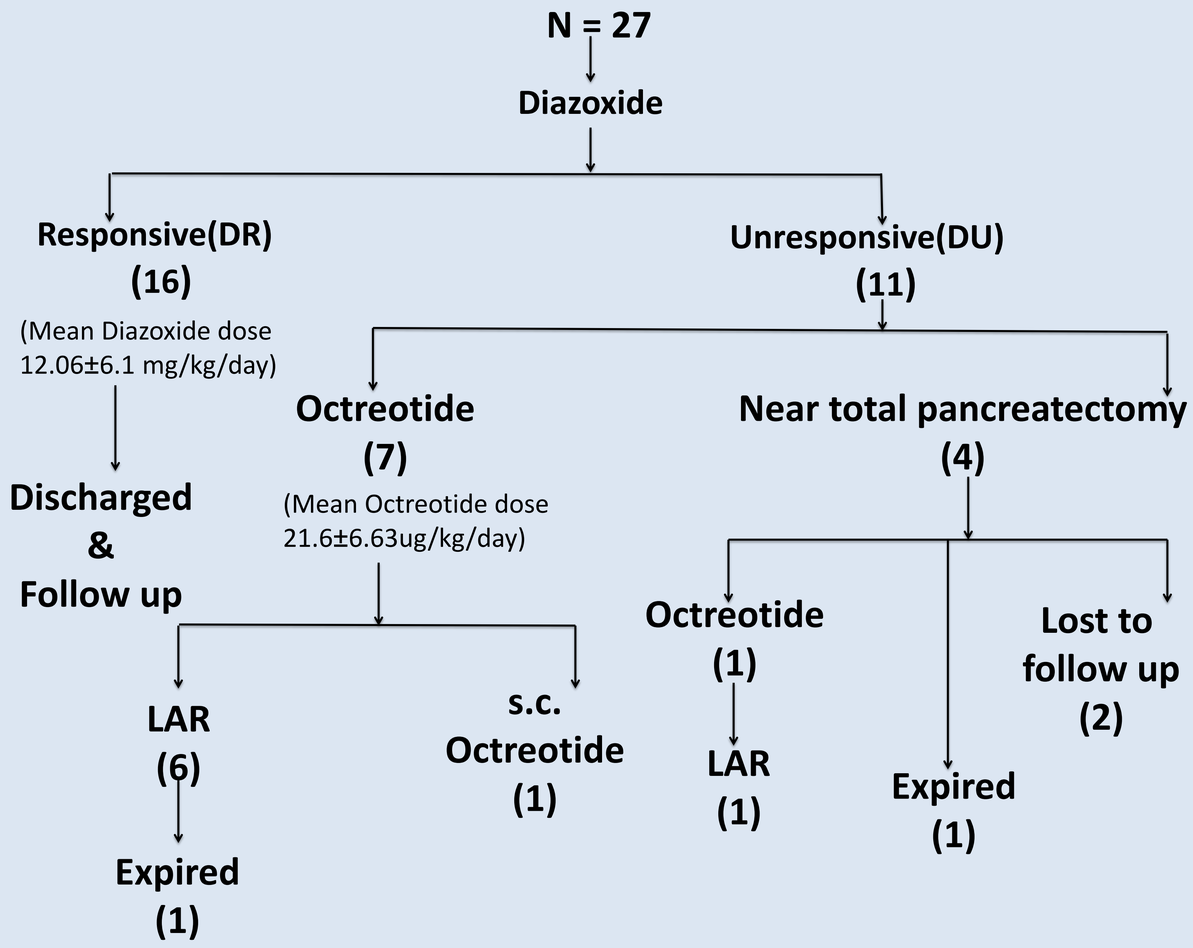
Materials and methods

- Records of 27(15 F) children diagnosed with hyperinsulinism in last 10 years were studied.
- Clinical , hormonal and mutation details were analyzed in **DR (Diazoxide Responsive**) and **DU (Diazoxide Unresponsive)** group.
- Syndromic and transient cases were excluded.

PATIENT CHARACTERISTICS (n=27)

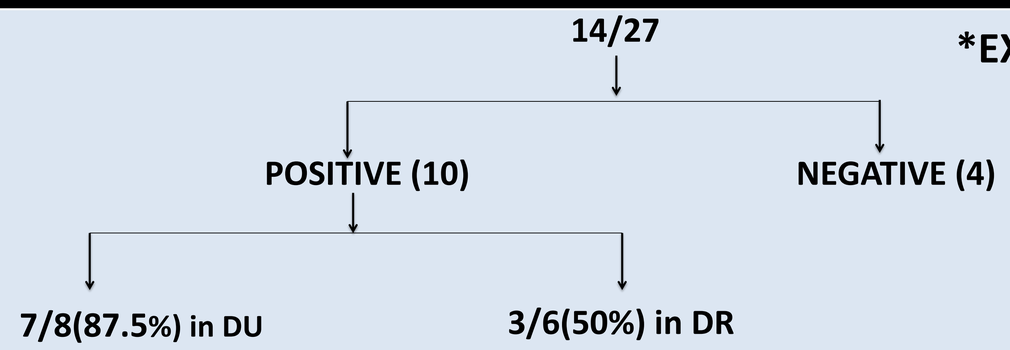
Females (n) (%)	15 (55)
Mean Gestational age ,weeks	37.3±0.99(36-40)
Mean Birth weight ,grams	3240±695 (1500-4600)
Median Age of onset ,days	3 (1- 240)
Diagnosed in neonatal period ,(n) (%)	20(74)
Large for gestational age,(n) (%)	9(33.3)
Consanguinity (%)	8(29.6)
Mean of maximum GDR(mg/kg/min)	12.6±4.81
Mean Blood glucose at diagnosis (mg/dl)	30±11.5
Mean Serum Insulin at diagnosis (mIU/ml) (range)	26.57 (3.6 - 300)

TREATMENT RESPONSE



MOLECULAR CHARACTERIZATION* (ABCC8 & KCNJ11)

*EXETER,UK



- 9 in ABCC8 gene , 1 in KCNJ11 gene
- 2 novel mutations – one in each ABCC8(p.V1361L) and KCNJ11(p.C142Y) gene.
- 1- de novo mutation
- 2 mutation positive children were infant of diabetic mother
- 3 – mutations were paternally inherited
- 3 – AD inheritance , all in DR group
- 6 were heterozygous , 4 were homozygous mutations
- 2 children had atypical features {one with MPHD(Empty sella syndrome) and one with dystonia and late onset hyperinsulinism)} – but were mutation negative

CHILDREN ON LONG ACTING OCREOTIDE (LAR)

- Mean duration of follow up – 12.25 months(6-24)
- Mean age at starting LAR - 8.38 months (1-33)
- Mean age at last follow up – 18.37 months(6-47)
- Mean dose of LAR at last follow up – 21.52 ± 5.2 ug/kg/day
- Daily Octreotide stopped on 2nd dose of LAR
- Mean Height SDS at last follow up- -0.9±1.92 ,
- Although 2 children had low IGF 1 level on follow up , all had normal growth velocity

Side effects

- Gall bladder pathology (5/8) . 3 had stones , 2 had sludge
  On Ursodeoxycholic acid , 40 % reduction in size of gallstones seen on follow up
- No significant differences in dose of LAR in patients with(23.40 ±4.15ug/kg/day) or without (18.40 ± 7.14ug/kg/day) GB pathology(p=0.35)
- Deranged liver functions with severe bacterial sepsis(1/8)

OUTCOME

33.3% (9/27) had normal milestones
59.2% (16/27) had delayed milestones with/without neurosensory affection
7.4% (2/27) expired

CONCLUSION

ABCC8 mutation was the commonest mutation found in our cohort.
40% of our children did not respond to Diazoxide of which 36% underwent near total pancreatectomy.
In all Diazoxide Unresponsive patients LAR was useful to maintain euglycemia.
Long term studies are required to emphasize the safety profile of LAR.

Reference

*Arya VB, Senniappan S, Guemes M, Hussain K. Neonatal hypoglycemia. Indian J Pediatr. 2014; 81:58-65.

Conflict of interest : None

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