and summative scores also correlate with GPA in the preclinical period.

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Ketotic Hypoglycemia in Children with Previous Transient Congenital Hyperinsulinism

Congenital Hyperinsulinism (CHI) is a major cause of neonatal hypoglycemia characterised by non-ketotic hypoglycemia. We describe the occurrence and higher prevalence of ketotic hypoglycemia (KH) in 5 children with transient CHI. Four children had required diazoxide to control the persistent hypoglycemia that was discontinued at a mean age of 11.25 (+5.25) months. KH developed after an average time period of 6.7 months following the resolution of CHI. Children with transient CHI may be at risk of subsequently developing KH at a variable age period.

Keywords: *Neonatal hypoglycemia, Ketotic hypoglycemia, Outcome*.

Congenital Hyperinsulinism (CHI) is a complex genetic disorder causing recurrent and persistent hypoglycemia, affecting 1in 50,000 children due to defective insulin secretion from pancreatic β-cells [1]. CHI, can be transient or permanent, and could be associated with overgrowth syndromes, birth asphyxia, IUGR, Rh isoimmunisation and maternal diabetes mellitus [2].

Ketotic hypoglycemia (KH*)* is the most common form of hypoglycemia beyond infancy, the exact etiopatho-genesis of which still remains obscure [3,4]. KH readily responds to oral or intravenous glucose administration without causing permanent neurological sequelae with majority of children outgrowing this condition with age. The development of KH after resolution of transient CHI has not been widely reported. We report our observations on KH after resolution of CHI.

After approval from the Institute's Ethics Committee the clinical data was collected from 142 children referred to our centre with persistent hypoglycemia between 2009 and 2016. Diagnosis of CHI (inappropriately high insulin and C-peptide and low Free Fatty Acids (FFA) and 3-betahydroxyl butyrate) and KH (low insulin and C-peptide with elevated FFA, 3-betahydroxybutyrate and normal cortisol during hypoglycemia [glucose <45 mg/dL]) were made based on clinical and biochemical parameters. Patients with CHI who developed KH subsequently were included in the study.

Five children (all boys) developed KH subsequent to resolution of CHI. Baseline characteristics of each child and time interval for development of KH are shown in ***Web Table* I**. The mean (SD) birthweight was 2.82 (0.45) kg and the mean age at the time of initial presentation was 46.8 hours. All patients required higher rates of glucose infusion [13.70 (1.57) mg/kg/min)] with a mean (SD) glucose concentraion of 1.98 (0.72) mmol/L. The biochemcial screen during hypoglycemia confirmed CHI (raised insulin concentration with suppressed FFA and 3- betahydroxyl butyrate). Four children required Diazoxide [7.38 (1.94) mg/kg/day] therapy which was discontinued at a mean (SD) age of 11.2 (5.25) months. KH developed after a mean duration of 6.7 months following resolution of CHI.

Our study revealed that some infants presenting with transient CHI have an increased risk of developing KH later in childhood. Majority of patients with CHI tend to be of transient nature with some requiring diazoxide therapy for variable time periods [5].

KH is typically seen in toddlers who miss meals owing to inter-current illness and develop hypoglycemia along with ketonemia and ketonuria. In our study, all 5 children presented with KH during intercurrent illneness. Christensen described failure of the adrenergic stress response during episodes of KH [6]. One of our patients had low cortisol but his short Synacthen test revelaed normal cortisol reserve.

Development of KH exclusively in males was a notable feature of our study; similar to a previous study [9], which showed that children of male gender and with low body weight have increased susceptibility to KH [7]. However, the exact mechanism behind this association; however, is unclear.

IUGR infants are known to be hypoinsulinemic, secondary to placental insufficiency producing diminished transplacental glucose transport which reduces protein and glycogen synthesis. Lower plasma concentrations of insulin and glucose produces a marked reduction in hepatic and muscle glycogen content [8]. The reason why only some newborns with IUGR develop CHI is unclear. Small sample size and retrospective nature were the major limitations of our study.

Patients with transient CHI need long term follow-up to enable early identification and appropriate management of KH.

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WEB TABLE I SALIENT FEATURES OF CHILDREN WITH KETOTIC HYPOGLYCEMIA FOLLOWING CONGENITAL HYPERINSULISM

Parameters	*Patient 1*	*Patient 2*	*Patient 3*	*Patient 4*	*Patient 5*
Gestational age (wks)	40	37	40	38	41
Birth weight (SD)	3.05 (0.98)	2.65 (-2.15)	2.8(-1.59)	2.2(-3.06)	3.4(-0.17)
Age at presentation, h	18	72	72	24	48
Peak GIR mg/kg/min	12.5	12	14	14	16
Treatment	Diazoxide	Polycal	Diazoxide	Diazoxide	Diazoxide
Age when diazoxide stopped (months)	4	3	16	11	14
DT	14	7	5	6	2
Glucose, mmol/L	2.2	0.8	2.7	2.3	1.9
Insulin, mU/L	<2	<2	<2	<2	<2
FFA, µmol/L	2104	3465	2469	2958	5772
3-hydroxy butyrate, µmol/L	1964	4600	1989	3374	3091
Cortisol, nmol/L	830	623	498	830	278
GH, µg/L	8.23	23.2	17.2	9.3	2.59
Lactate, 0.7-2.1mmol/L	1.0	1.2	1.4	1.9	1.0

CHI-Congenital Hyperinsulinism; GIR-Glucose Infusion Rate; FFA- Free Fatty Acids, GH - Growth hormone, DT= time interval in months between resolution of CHI and the onset of KH.