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Original Article

Clinical Characteristics and Neurodevelopmental Outcome in Children with Congenital Hyperinsulinism in Resource Limited Settings

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Abstract

Objective: This study was conducted to describe the clinical characteristics of persistent Congenital Hyperinsulinism (CHI) and evaluate neurodevelopmental outcome and its risk factors in a cohort of Pakistani children.

Methods: This was a cohort observational analytical study carried out at the Pediatric Endocrinology Department, The University of Child Health Sciences, The Children's Hospital Lahore. Total 29 patients fulfilling the inclusion criteria were included in the study. Biochemical profile was recorded including serum insulin levels, C-peptide level, blood or urinary ketones. All children had their first assessment at the time of enrolment in study. Further follow up and neurodevelopment assessment was done at 6 months and one year after the first visit. Neurological assessment was done by the neurologist using TINE score (Touwen Infant Neurological Examination) for children who are younger than 2 years and by Hadders-Algra score for older children.

Results: Among children 65.6% presented with early onset of disease (<30 days) and with severe disease, 58.6% children were treated with octreotide while the remaining 34.48% children were treated with oral diazoxide. None of the children underwent surgical treatment. Abnormal neurological examination was noted in 55.17% children, 16.67% children had abnormal EEG findings, 33.3% children echocardiography findings were abnormal, as suffering from congenital heart disease, and 18.18% of children MRI findings were abnormal. Children with abnormal neurological assessment had severe disease, delayed referral to tertiary care hospital, longer admission duration, high frequency of worse symptoms, high frequency of abnormal EEG and MRI findings.

Conclusion: The prompt management of newborn hypoglycemia is essential for the fruitful outcome. Improving healthcare personnel knowledge and comprehension care of newborn hypoglycemia, implementing standardized neurodevelopmental testing, and determining causal relationship of congenital heart disease in CHI is necessary.

Keywords: Congenital hyperinsulinism, Hypoglycemia, Neurodevelopment, Diazoxide

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Introduction

Congenital hyperinsulinism (CHI) is a disorder which is quite rarely encountered and it is caused by excessive secretion of insulin by beta cells of pancreas.[1] CHI leads to hypoglycemia and fits in neonates and infants which can affect the long term development of brain with serious consequences if not properly treated.[2] Persistent congenital hyperinsulinism is a genetic disorder with an incidence of 1:50,000 live births in different countries and ethnicities but higher incidence has been reported in populations with higher rates of consanguineous marriages. No data is available about its incidence in Pakistan.[3-5] CHI is a monogenic disorder, and more than a dozen genes have been identified till date which are associated with CHI. The most commonly identified genes being ABCC8 or KCNJ,[11] which encode subunits of KATP channels involved in insulin release from pancreatic beta cell.[6]

CHI can be classified based on histology into 3 types. Focal form which is 30-40% of cases, diffuse form which is present in 60-70 % of patients or atypical histology which doesn't fit in the two categories[7]. Focal and

diffuse forms differ in symptomatology, treatment options and outcome. Focal form is caused by mutation in ABCC[8] or KCNJ[11] which is paternal in origin and heterozygous in character. It is curable in about 97 percent of cases by focal resection of involved segment of pancreas.[7] The diffuse form of CHI is caused by compound heterozygous, or homozygous mutations in ABCC[8] or KCNJ[11]. Many of these patients respond to medical therapy while pancreatectomy is needed in selected cases who don't respond to drugs.[8]

Prolonged hypoglycemia leads to neuronal injury as brain utilizes glucose for its fuel of metabolic processes. Furthermore, hyperinsulinism during hypoglycemia prevents the ketones from being utilized as an alternative source of energy by the brain. This increases the injury to the developing brain resulting in developmental delays and neurologic sequalae in a large proportion of patients.[9,10] Abnormal neurodevelopmental outcome has been reported in 26-48% of patients with permanent CHI and about 30% of children with transient CHI.[10,11] Epilepsy, visual problems, and infantile spasms have also been reported in CHI.[12] When it comes to clinical features and neurodevelopmental consequences, congenital hyperinsulinism (CHI) presents several difficulties in environments with low resources. If the disorder is not identified and treated promptly, it may cause serious neurodevelopmental delays. The illness is characterized by excessive insulin production that results in chronic hypoglycemia. This study aims to describe the clinical features, biochemical profiles of persistent CHI, and to evaluate neurological outcome including minor neurological dysfunction.

Methods

This was a cohort observational analytical study carried out at the Pediatric Endocrinology Department, The University of Child Health Sciences, The Children's Hospital Lahore from November 2022 to

August 2024. Approval from hospital ethical committee was sought. Informed written consent was taken from patient's parents participating in this study.

A total of 29 patients were included in the study based on a predefined inclusion and exclusion criteria as following. All children from neonatal age up to age of 16 years and having following characteristics were included in study (hypoglycemia defined as plasma glucose ≤ 50 mg/dl, detectable insulin level >1uU/ml or C-peptide level ≥0.5ng/ml, Hypoketonemia (BOHB <1.8mmol/L) or nil urinary ketones, and Glucose infusion rate >8mg/kg/minute). Following patients were excluded from the study; children suffering from severe birth asphyxia or intracranial hemorrhage need admission, children suffering from Inborn error of metabolism or neurodegenerative disorders, brain malformations, storage disorders like GSD (glycogen storage disorder), children suffering from hypoglycemia due to other hormone deficiencies, preterm newborns below 34 weeks' gestation.

Every child was assigned a serial number. Detailed history was taken, and all the information was noted. Data was recorded regarding gestational age, birth weight, gestational diabetes, age of diagnosis, consanguinity, gender, main presenting symptoms, duration of admission.

Profile was also recorded including serum insulin levels, C-peptide level, blood or urinary ketones. All children had their first assessment at the time of enrolment in study. Further follow up and neurodevelopment assessment was done at 6 months and one year after the first visit. Neurological assessment was done by the neurologist using TINE score (Touwen Infant Neurological Examination) for children who were younger than 2 years and by Hadders-Algra score for older children. According to TINE and its modified form, children were into 4 divided groups:

- normal group 0 who do not have any minor neurological dysfunction (MND),
- Group 1 normal suboptimal 1-2 dysfunctional clusters,
- Group 2 MND group who have evidence of neurological dysfunction in at least three areas and
- Group 3 grossly abnormal i.e., clear neurological syndrome.

Infant stimulation test and Portage guide for early education PGEE score was used for assessing development in children below 6 years of age and by intelligence quotient (IQ) for those above 6 years of age.[14] All children having any sort of neurological impairment were considered as one group and their clinical characteristics were compared with children who were free of any neurological sign and symptoms. The two groups were compared with regard to factors leading to neurological impairment. Diazoxide was given in dose of 5-15mg/kg/day along with hydrochlorothiazide 1.5-2.5mg/kg/day. Octreotide was used in dose of 5-35mcg/kg/day in divided doses every 6 to 8 hours.

Treatments were entered in patients' medical records. Children were observed for side effects of above-mentioned drugs. Diazoxide unresponsiveness was labelled if there was no response to diazoxide on 15-20mg/kg/day for 5 days. The growth parameters of the child were followed 6 monthly in the form of height, weight, occipitofrontal circumference (OFC).

Data was analyzed by using SPSS (Statistical Package of Social Sciences) program version 25. Qualitative data will be presented in number or percentage. Student

t-test was used to compare quantitative variables for patients with normal and abnormal neurological findings and chi-square test was used to compare qualitative variables. The threshold of significance in this study was fixed at <0.05.

Results

Table-1 describes the demographic, duration of diagnosis, clinical symptoms, severity of disease, age at diagnosis duration between diagnosing and symptoms, clinical characteristics, medical management, its res-

Table 1: *Characteristics of Patients (n=29)*

Characteristics		Outcome n (%) or Mean±SD
Gender (Male/Female)		15/14(51.7/48.3)
Weight (Kg) (n=23),		3.46±1.10 (1.50-6.0)
Gestational Age (Weeks) (n=28)		37.07±2.38 (28-38)
Age (Days), mean±SD		
Duration between symptom till referral to tertiary center (Days)		35.26±105.32 (0.02-540)
Main presenting Symptoms	**Hypoglycemia Seizure**	25(86.2)
	Apnea	12(41.4)
	Loss of consciousness	10(34.5)
Disease Onset	Early (<30 days)	19(65.6)
	Late (>30 days)	10(34.4)
Severity of Disease	Non-Severe	9(31)
	Severe Disease	19(65.5)
	Age at Diagnosis days (mean±SD, Range)	139.58±352.57(0.20-1825)
	Duration between symptoms & diagnosis days (mean±SD, Range)	73.78±111.36 (5-540)
	Admission duration (mean±SD, Range)	17.93±13.34 (2-45)
	Lowest recorded blood glucose level mg/dl	21.50±7.92 (10-37)
	Serum insulin level mIU/ml	18.10±16.45 (1.15-67.40)
	Consanguinity	22(75.9)
	Family history of hypoglycemia	5(17.24)
Hyperinsulinism Treatment Plan	Diazoxide on current treatment [5.58±1.96 mg/kg/day, Min=3, max=9.3, 8-12 Hours]	10(34.48)
	Octreotide on current treatment [8.22±3.60 mcg/kg/day, Min=4, Max=16, 4-8 hours]	18(58.6)
	Fantomalt (Food fortification)	1(3.45)
	Octreotide+ Diazoxide	1(3.45)
	Medication stopped due to recovery	1(3.45)
Diazoxide	**Trial Given**	22(75.86)
	(Trial not given)	6(20.69)
	(Unresponsive)	7(24.14)
	(Stopped due to side effects)	2(6.90)
	Treatment Response	15(51.72)
Side Effects	**Fluid Retention**	2(6.90)
	Hypertrichosis	9(31.03)
	Pulmonary Hypertension	3(10.34)
	Growth Suppression	2(6.90)
	Gall stone	1(3.45)
	Surgical Treatment (Pancreatectomy)	0(0)
Echocardiography Findings (n=25)	**Abnormal (congenital heart disease)**	8(32)
	Normal	17(68)
	Hypoglycemic episodes	15(51.7)

ponse and side effects. Table-2 describes the neurological examination of the patients, further evaluation of abnormal neurological findings evaluation, assessment of developmental abnormalities and patients who underwent EEG and MRI

Table 2: *Neurological outcome*

Variables	Outcome	Frequency (%)
Neurological Examination (n=29)	Normal	10(34.48)
	Abnormal	16(55.17)
	Clear neurological syndrome (Grossly abnormal)	9(56.25)
	MND>2 abnormal areas	5(31.25)
	Normal suboptimal (1 -2 Dysfunctional clusters)	2(12.50)
		Not done
	Mortality	2(6.89)
	Lost to follow up	1(3.45)
Developmental Assessment (n=29)	Cerebral palsy (Spastic quadriplegic)	3(10.34)
	Diplegic	1(3.45)
	Hemiplegic	1(3.45)
	Ataxia	1(3.45)
	Borderline delay	3(11.11)
	Speech delay	2(6.90)
	GDD	13(44.82)
	Mild GDD	3(10.34)
	Moderate GDD	1(3.45)
	Normal	10(34.48)
	Mortality	3(10.34)
	Lost to follow up	1(3.45)
EEG Findings (n=11)	Normal	9(75)
	Abnormal	2(16.67)
	Focal Epilepsy	5(45.45)
	Generalized	6(54.55)
	Anti-Epileptic Drug (epileptic children)	7(24.1)
	Settled	2(18.18)
MRI Findings (n=11)	Normal	9(81.82)
	Abnormal	2(18.18)
Echocardiography Findings (n=24)	Normal	16(66.67)
	Abnormal	8(33.33)

All our patients responded to drug therapy (octreotide and diazoxide). Among 29 patients, 10 are on diazoxide, 18 are on octreotide and one case went into remission. In our clinical settings we are using octreotide as fist line therapy as diazoxide is not easily available in Pakistan. Octreotide subcutaneously was started as initial treatment in emergency in all patients being treated for acute episodes of hypoglycemia, and later a trial of diazoxide given in combination with octreotide to 22 patients and 06 infants were not started diazoxide due to congenital heart defects, 01 refused. In children showing response to diazoxide, octreotide was gradually tapered down. Out of 22, 15 patients were responsive to diazoxide with stoppage of octreotide (68%), we had to stop diazoxide in 2 patients due to side effects and parental concerns. Among side effect, the most common was hypertrichosis followed by fluid retention. The mean dose of diazoxide for the patients in this study was 5.58± 1.96 mg/kg/day which was quite less as reported in previously published studies. The mean dose of octreotide was 8.22±3.60 mcg/kg/day in our study population.

Neurological assessment was found to be abnormal for 16(55.17%) children. Among these the most common abnormality was clear neurological syndrome followed by MND>2 abnormal areas (assessed with TINE score) and normal suboptimal abnormality. Portage guide for early education PGEE score was used to assess the development. As per this criterion 8 children were Global developmental Delay(GDD), 3 children were Spastic Cerebral Palsy, and 2 children had only speech delay.

Among these patients 7 children were on anti-epileptic therapy and 2 children stopped medication due to their recovery.

Table 3 describes the comparison of patients' characteristics in relation to their neurological examination. Patient characteristics include demographic as well as clinical parameters, presenting symptoms, age at diagnosis, blood glucose level, parental history of marriage, family history of hypoglycemia, treatment outcome and investigations findings (EEG and MRI).

Discussion

An uncommon genetic condition known as congenital hyperinsulinism (CHI) is characterized by extreme hypoglycemia and uncontrolled insulin production. There are not many studies on CHI patients from our clinical setup. In this study a total of 29 patients were included. Among patients, 15(51.7%) were male and 14(48.3%) were female. The existing literature suggests that congenital hyperinsulinism does not exhibit a strong sex predilection. Epidemiological studies have found that the disorder affects both males and females at roughly equal rates, with no significant differences in prevalence based on biological sex.[13] Male gender, late age upon presentation, and severity of CHI all increase the chance of poor outcomes.[14]

Wafaa Laimon et al, study reported male to female ratio as 1.5:115. In our study 65.6% patients had disease onset <30 days and 34.4% patients had disease onset >30 days. Studies have reported variable results regarding early onset of disease ranging between 45%-80% of the patients.[15-17] Amalie G. Rasmussen et al, reported 62.5% of the patients presented early onset (<30 days).[16] In this

Table 3: *Comparison of Patient characteristics with normal and abnormal neurological findings*

		Neurological Assessment		p-value
		Normal (n=11)	Abnormal (n=16)	
Gender				
Male		3(27.3%)	10(62.5%)	0.072
Female		8(72.7%)	6(37.5%)	
Age at presentation (days)		28.11±32.30	14.78±20.87	0.203
Gestational Age		36.63±2.37	37.31±2.49	0.487
Birth Weight		3.16±1.17	3.48±0.87	0.486
Duration between symptom till referral to a tertiary center (Days)		n=8	n=16	0.034(a)
		6.87±11.24	57.93±135.24	
		0.70[12.34]	7.00[43]	
Presenting Symptoms				
Hypoglycemia		9(81.8%)	12(75%)	0.675
Seizure		10(90.9%)	13(81.3%)	0.624
Apnea		0(0%)	1(6.3%)	0.398
Severity	Non-Severe	3(27.3%)	6(37.5%)	0.692
	Severe Disease	8(72.7%)		
Loss of consciousness		3(27.3%)	8(50%)	0.427
Age at Diagnosis days (Hyperinsulinism)		314.86± 603.37	124.64±202.34	0.250
Admission Duration (days)		15.36± 15.04	18.94±12.40	0.506
Lowest recorded blood glucose level (mg/dL)		20.33±7.88	21.50±7.97	0.743
Serum insulin level miU/ml		21.86± 18.32	16.19±15.86	0.400
Consanguinity		7(63.6%)	14(87.5%)	0.187
Family history of hypoglycemia		2(18.18%)	3(18.75%)	0.975
Treatment	Surgical Treatment	0(0%)	0(0%)	-
	Medical Management	11(100%)	16(100%)	
EEG (Test Done)		1	10	
Abnormal		0(0%)	2(20%)	
MRI (Test Done)		2	9	0.345(F)
Abnormal		1(50%)	8(88.9%)	

Note (a): Mann Whitney u test

study most frequent presenting symptoms werre hypoglycemic seizures (86.2%) followed by apnea (41.4%) and loss of consciousness (34.5%). The study carried out in Egypt showed the most common presenting symptom as seizure (92.8%) followed by apnea (4.8%) and loss of consciousness (2.4%).[15] Aijing Xu et al. reported that seizure was seen in 61.53% of the patients in his study.[17] In the present study 65.5% of the cases presented with severe disease. Similar findings were reported by previously published studies. Helleskov A in his study reported that 72% of the cases presented with severe disease.[18] The percentage of children with severe disease was 52% in the study on Egyptian cohort.[15] So, our study findings are in agreement with previous studies where the majority of children had severe disease. Diazoxide is the first-choice medication in conservative therapy; nonetheless, a large proportion of patients do not respond to treatment or respond only partly.[19-21] In our study majority of the patients were treated with octreotide as first line therapy due to non-availability of diazoxide and on availability shifted to diazoxide in combination with food fortification (fantomalt, maltodextrin a polysaccharide and digestible starch). Diazoxide was ineffective in 24.14% patients, the treatment response was seen in all patients with medical management of octreotide and diazoxide and children were able to maintain blood glucose between 70 to 100mg/dl with drug therapy. Studies have reported that those patients who were unresponsive to the medical management were treated surgically. A previous study reported 50% success rate with medical management.[15] In the same study half of the patients (50%) underwent pancreatic surgery. However, none of the patients in present study underwent surgical intervention. Another major limitation of this study was that we were not able to perform 18-Fluro Dopa PET scan for the children due

to non-availability (which is a major limitation in performing focal surgery).

Lack of expertise and parental concern was one reason for not performing pancreatectomy in our cohort.

Hypoglycemia complications include seizure, developmental delay, and irreversible brain damage. Therefore, preventing hypoglycemia in these patients is the treatment objective for reducing morbidity and death. The most frequent side effects seen among patients was hypertrichosis (31.03%) followed by pulmonary hypertension (10.34%), fluid retention (6.90%) seen as side effects of diazoxide and growth suppression (6.90%), gall stones (6.90%) with octreotide. In one previous study, hypertrichosis was the most frequent side effect followed by salt and water retention among patients who were treated with diazoxide.[15]

Despite advances in medical therapy, a considerable number of children with Congenital Hyperinsulinism (CHI) have severe neurodevelopmental defects[14]. Identifying neurodevelopmental outcomes is a priority for children in follow-up care; children with developmental problems may need more assistance with physical and cognitive limitations.[14]

Insufficient stability of plasma glucose levels, delayed diagnosis, and neonatal beginning of the illness are recognized risk factors linked to worse neurodevelopmental outcomes in children with CHI. In this study neurological examination (assessed with TINE score by the neurologist) was abnormal among 16 (55.17%) patients. In another study neurological impairment was reported among 55% patients which is similar to this study.[15] In another study neurological impairment was found to be 38% among patients[16]. Neurological deficits in CHI patients showed variable prevalence in different study from different countries ranging from 18%- 47%.[22-24] In our study the neurological impairment is 55.17%, the most frequent abnormal neurological finding among patients was abnormal clear neurological syndrome (56.25%) followed by >2 dysfunctional clusters (31.25%) and 2 dysfunctional clusters (12.50%). The developmental assessment showed that 10.34% patients had spastic quadriplegic cerebral palsy, 44.82% had GDD, and 11.11% had borderline delay, one child was hemiplegic CP and one diplegic CP.

Wafaa Laimon et al, in her study used Denver's test for neurological assessment. As per her findings 36% of the cases had neurocognitive problems including 31% with global developmental delay, one patient had speech delay and one patient had IQ less than 7015. Studies have used different diagnostic criteria for assessment of neurological examination. The variation in results may be due to difference in assessment criteria. The risk of neurodevelopmental damage was elevated not only by very low blood glucose but also by inadequate treatment, as seen by the delay in seeking hospitalization at an expert clinic.[25] These factors were observed in this study among patients with abnormal neurological findings. The high rate of developmental delay in this study is likely to be due to the delayed diagnosis. The primary mechanism by which congenital hyperinsulinism can precipitate neurological impairment is the detrimental impact of sustained hypoglycemia on the brain. The brain is highly sensitive to variations in glucose levels, and prolonged exposure to low blood glucose can lead to neuronal damage and dysfunction. Various factors, including low blood ketones, genetic disorders, neurotoxins, prolonged hypoxia can contribute to the development of neurological disorders in children with congenital hyperinsulinism. 7 of our children (24.1%) were declared epileptic and are taking antiseizure medications, two children were weaned off from antiepileptic drugs. The frequency of epilepsy is quite high in CHI patients and this should not be ignored.

Children who were neurologically abnormal had markedly significant delay in referral to tertiary hospital, mean 57.93 days versus normal children 6.87 days and p value was significant at 0.03. The neurologically abnormal children had longer admission duration; 18.94 versus 15.36 days.

Congenital heart disease was also a frequent finding in CHI children with 33.33% suffering from various types of congenital heart diseases including 3 with VSD, 3 patients of PDA and 2 with pericardial effusion. Therefore, echocardiography should be done in all children of CHI to find its causal relationship and it may be more desired especially in children before and during treatment with diazoxide.

This study has certain strengths which are that it is the first of its kind in our clinical setting in which detailed presentation, management and neurological assessment was done for CHI patients. Mortality rate was very low with current management protocol. The limitations of the study are a small sample size, duration of study, and that the study was single center. Genetic assessment was not carried out in all patients due to resource limitation.

Conclusion

The prompt management of newborn hypoglycemia is essential for the fruitful outcome. Improving healthcare personnel knowledge and comprehension, care of newborn hypoglycemia, CHI, and national guidelines on the condition is necessary to enable prompt identification and appropriate management. Standardized neurodevelopmental testing should be conducted in all children with chronic and transient CHI at varying ages and developmental stages. Congenital heart disease

was quite frequent in CHI patients, early screening should be done for congenital heart disease and extended studies need to see its causal correlation.

Ethical Approval: The IRB/EC approved this study via letter no. 688/CH-UCHS dated September 09, 2023

Conflict of Interest: None

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Authors' Contribution

MAK: Conceptualization of the project

JM, SA: Design of the work.

MZ, JRA, MSA: Data acquisition, analysis, or interpretation.

JM, MZ, JRA, MSA: Draft the work.

MAK, SA: Critical review of important intellectual content.

All authors approve the version to be published.

All authors agree to be accountable for all aspects of the work.

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