European Journal of Pediatrics (2020) 179:947–952
https://doi.org/10.1007/s00431-020-03581-z

ORIGINAL ARTICLE

Congenital hyperinsulinism: management and outcome, a single tertiary centre experience

K. El Tonbary[1,3] · P. Robinson[2] · I. Banerjee[4] · M. G. Shaikh[1]

Received: 27 July 2019 / Revised: 9 January 2020 / Accepted: 15 January 2020 / Published online: 30 January 2020

Abstract

Hyperinsulinemic hypoglycaemia (HH) is the most frequent cause of persistent hypoglycaemia in neonates and infants. The most severe forms of HH are inherited and referred to as congenital hyperinsulinism (CHI). Diazoxide is the mainstay of treatment, with surgery being an option in appropriate cases. To describe the management and outcome of patients with CHI within our service. Children referred to or attending HH clinic between 2009 and 2017 were identified. Clinical course, genetics and interventions were documented. A total of 39 children were identified, and seven patients with secondary and syndromic HH were excluded. Most were born with an appropriate weight for gestational age (62.5%). Diazoxide was started in all patients; however, 7 did not respond and required octreotide/continuous feeding, with 6/7 requiring surgery. Genetic mutations were detected in 12/32 (37.5%). Hyperinsulinism resolved in conservatively treated patients within 12 months in 11/32 (34.3%) compared to 14/32 (43.7%) requiring more than 12 months of medication. A total of 7 patients underwent pancreatectomy.

Conclusion: Although LGA and SGA are risk factors, most babies in our cohort are born AGA. A genetic mutation does not exclude medical remission; long-term conservative treatment of CHI is feasible as surgery does not guarantee complete remission.

What is Known:
- *Congenital hyperinsulinism (CHI) is a clinically and genetically heterogeneous disorder that is the most common cause of permanent hypoglycaemia in infants and children.*
- *Identification of genetic mutations and the use of 18F-DOPA PET scan when feasible lead to better outcomes.*

What is New:
- *The study describes clinical criteria, management and outcome of large number of patients with CHI in single tertiary centre.*
- *Conservative treatment is feasible without the need for surgery, with HH resolving in over 30% within 12 months, irrespective of genetic mutation.*

Keywords Congenital hyperinsulinism (CHI) · Diazoxide · 18-F-DOPA PET/CT scan · KCNJ11 · ABCC8 · GLUD1

Abbreviations

AGA	Appropriate for gestational age
CHI	Congenital hyperinsulinism
HH	Hyperinsulinemic hypoglycaemia
LGA	Large for gestational age
PEG	Percutaneous endoscopic gastrostomy
PET	Positron emission tomography
SGA	Small for gestational age

Communicated by Peter de Winter

✉ K. El Tonbary
khadigadoc@yahoo.com

P. Robinson
peter.robinson3@nhs.net

I. Banerjee
Indi.Banerjee@mft.nhs.uk

M. G. Shaikh
guftar.shaikh@nhs.net

[1] Department of Endocrinology, Royal Hospital for Children, Glasgow, UK

[2] Department of Metabolic Medicine, Royal Hospital for Children, Glasgow, UK

[3] Department of Paediatric, Ain Shams University, Cairo, Egypt

[4] Department of Endocrinology, Manchester Children's Hospital, Manchester, UK

Introduction

Hyperinsulinemic hypoglycaemia (HH) is the most frequent cause of persistent hypoglycaemia in neonates and infants. The most severe forms of HH are inherited and the term congenital hyperinsulinism (CHI) refers to this form. HH can be secondary to various risk factors like perinatal asphyxia, maternal diabetes, intrauterine growth restriction and maternal medications. Various developmental syndromes like Beckwith-Wiedemann, Kabuki or Sotos syndrome have also been associated with HH [1, 2].

CHI compromises a group of different genetic disorders with the common finding of recurrent episodes of hypoglycaemia due to inappropriate insulin secretion. The estimated incidence of CHI is 1/50,000 live births and up to 1/2500 in areas with high rates of consanguinity [3]. Mutations in key genes, which play a role in the regulation of insulin secretion, constitute the underlying molecular genetics of CHI. Mutations in 12 different genes (*ABCC8, KCNJ11, GLUD1, GCK, HADH*, *SLC16A1, UCP2, HNF4A HNF1A, HK1, PGM1* and *PMM2*), that lead to dysregulated insulin secretion, had been described [2]. Recently, mutations in two novel genes have been linked to CHI: calcium voltage-gated channel subunit alpha1 D (*CACNA1D*) and forkhead box A2 transcription factor (*FOXA2*) genes [4].

In the last decade, more than 200 different mutations in *ABCC8* compared to 30 distinct *KCNJ11* mutations, which respectively encode for the *SUR1* and *Kir6.2* subunits of the K-ATP channel, were estimated to account for 40–45% of CHI cases (82% of diazoxide-unresponsive patients) [5], whereas mutations have been identified in other genes in approximately 5 to 10% of the cases. The aetiology for the remaining 40% of patients was still unknown [6].

Hypoglycaemia is the main feature of CHI with a high risk of seizure and neurological damage. Symptoms of hypoglycaemia are diverse and vary according to the severity and age of patient. They range from asymptomatic, incidental finding on routine glucose monitoring to life threatening apnea, coma or status epilepticus [3]. The clinical presentation is most severe in the new-born period and may be quite subtle later in infancy and childhood. Even within same family, the severity of the disease can vary substantially [7]. The early diagnosis and immediate meticulous management are the corner stones for preventing brain injury in patients with CHI.

Diazoxide is the mainstay of medical treatment and first-line therapy. It is a ligand of the K-ATP which activates intact K-ATP channels reversing glucose-induced channel closure. Diazoxide is ineffective in diffuse CHI due to recessive inactivating mutations of *ABCC8* and *KCNJ11* and in patients with focal CHI [8].

Recent advances in molecular genetic analysis and 18-fluro L-dihydroxy phenylalanine (^{18}F-DOPA) positron emission tomography (PET CT) imaging have fundamentally changed the clinical approach to patients with CHI and paternally inherited mutations, especially in *ABCC8* gene, who more likely harbour a focal lesion on the scan [9, 10].

The aim of the study was to assess the management and outcome of patients with CHI referred to Royal Hospital for Children, Greater Glasgow and Clyde.

Methods

This is a retrospective study of children referred to or attending our tertiary endocrine service with refractory hypoglycaemia and documented CHI between 2009 and 2017.

Diagnosis was based on documented hypoglycaemia, in the presence of an intravenous glucose infusion rate of > 8 mg/kg/min, and/or detectable insulin or C-peptide levels with low free fatty acids and low ketone bodies.

Gestational age, age at presentation, perinatal risk factors, family history, birth weight, maximum glucose infusion rate and initial laboratory investigations were all recorded. Diazoxide responsiveness and side effects, together with the use of other medications and surgical intervention, were also documented. Genetic analysis was performed in the Exeter Molecular Genetic Laboratory using custom designed Agilent SureSelect Target Enrichment which allows detection of base substitutions (SNVs), small insertions and deletions (indels) and partial/whole gene deletions and duplications (CNVs), after obtaining written informed consent from parents.

Patients with developmental delay or behavioural disorders have been assessed through Child Development services.

Statistics

Chi-square test and Mann-Whitney test were used for data analyses, using IBM SPSS (version 22.0). Significant level was set as $p < 0.05$.

Results

A total of 39 patients (25 males) were identified during study period (Fig. 1). The median of their current age is 2.42 years (range 0.16–20.36).

All had documented HH. Six patients had risk factors (intrauterine growth restriction, small for gestational age (SGA), maternal beta-blockers), required limited diazoxide treatment (< 3 months), had no genetic analysis performed and therefore classified as secondary hyperinsulinism. One patient with Beckwith-Wiedemann syndrome was also excluded.

Clinical characteristics

Regarding the other 32 patients, 26 (81.2%) presented within the first 72 h of life and 27 (84.3%) were born at term. Birth weight ranged between 1916 and 4610 g with a median of 3201 g. Of the 32 patients, 20 (62.5%) were born with an appropriate weight for gestational age (AGA), 5 (15.6%) were large for gestational age (LGA), and one being macrosomic (birth weight > 4500 g (as defined by American College of Obstetricians and Gynecologists)).

Maximum glucose requirement ranged between 6.7 and 18.8 mg/kg/min (median 13.1 mg/kg/min). Insulin and /or C-peptide levels were measured in 28, with 25 having insulin and three with C-peptide alone. Insulin or C-peptide levels were not available in four patients. In these four patients, CHI was diagnosed based on high glucose requirement, low FFAs and low serum ketones in the presence of hypoglycaemia. Insulin levels ranged from 1.3 to 110 mIU/L (median of 11.95 mIU/L).

Management

Diazoxide was started in all patients with most (27) having a baseline echocardiogram and most responding well to treatment. Seven did not respond to diazoxide and required octreotide and/or percutaneous endoscopic gastrostomy (PEG) tube feeding. Six of them ended up requiring surgery.

Adverse effects secondary to diazoxide therapy were observed in four patients, mainly pulmonary hypertension/fluid overload in 3/4, with ileus in the other patient. Diazoxide was discontinued in patients who developed pulmonary hypertension and they were managed with octreotide and/or high caloric intake.

Genetic mutations were detected in 12/32 (37.5%) (*KCNJ11-5*, *ABCC8-4* and *GLUD* 1-3) (Table 1).

K-ATP channel mutations were heterozygous (monoallelic) except in two siblings of consanguineous parents who had a novel homozygous missense mutation (*KCNJ11-A161V*).

Patients with genetic mutations were mainly males 8/12 (66.6%) and born AGA 9/12 (75%) compared to 10/20 (50%) and 11/20 (55%) respectively in those with no gene mutation with no significant difference in birth weight between both groups ($p = 0.223$) (Fig. 2).

^{18}F-DOPA PET CT scan was performed in all seven patients with paternally inherited mutations of the *ABCC8* and *KCNJ11* genes and two diazoxide-unresponsive patients requiring PEG and/or octreotide and having no identifiable mutation.

CHI resolved within 12 months in 10/32 (31.25%) including three patients with paternally inherited *KCNJ11* mutations, all of which had undetectable focal lesions on ^{18}F-DOPA PET CT and did not require surgery.

14/32 (43.75%) required more than 12 months of medication with 10/14 having no identifiable mutation.

There was no correlation between the presence of gene mutation and treatment duration ($p = 0.687$). Also, maximum glucose infusion rate and insulin levels at diagnosis had no significant correlation with the duration of medical treatment ($p = 0.423$ and 0.341 respectively).

A total of seven patients underwent pancreatectomy, three had subtotal/near-total pancreatectomy in early infancy and still required medical treatment post pancreatectomy. The one who required near-total pancreatectomy had diffuse disease due to homozygous *KCNJ11* novel missense mutation and still required octreotide postoperative, developing diabetes at age of 9 years (his sibling with same mutation was managed conservatively on combination of octreotide subcutaneous injections and overnight frequent bolus feeding through PEG tube). Four patients had focal pancreatectomies, three had paternally inherited mutations (*ABCC8*) and one with focal lesion, but no mutation identified. Neurodevelopmental deficits and behavioural disorders were detected in 6/32 (19%). Two have global developmental delay, three diagnosed with autistic

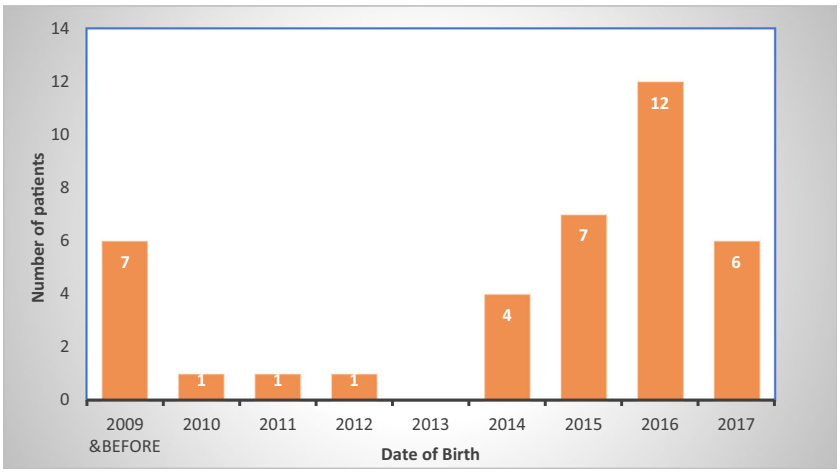

Fig. 1 Patient referred to hyperinsulinism clinic during study period

Table 1 Characteristics of patients with genetic mutations

	Age at presentation	Gestational age (weeks)	Birth weight (grams)	Weight for age	Diazoxide response	Need for other medication	Gene	PET Scan	Surgery	Outcome
1	15 weeks	40	3728	AGA	Unresponsive	Octreotide	Heterozygous missense mutation, *ABCC8*	Focal lesion	Large focal lesion excised.	Off medication
2	Day 3	36	3800	LGA	Unresponsive	Octreotide	Homozygous missense mutation, *KCNJ11*	No	Near-total pancreatecto-my*	Medical treatment (octreotide) for 8 years Diabetes at age 9 years
3	Day 1	37	3762	LGA	Unresponsive	Octreotide/PEG	Homozygous missense mutation, *KCNJ11*	No	No	On treatment
4	Day1	40	3700	AGA	Unresponsive		Heterozygous mutation, *GLUD1*	No	Subtotal pancreatecto-my*	Restarted diazoxide and discontinued at age 18 years
5	Day 1	39	2530	SGA	Developed side effect	High carbohydrate	Heterozygous mutation, *KCNJ11*	Heterogeneous	No	Stopped/age 6 months
6	Day 1	41	3275	AGA	Developed side effect	Octreotide	Heterozygous mutation, *KCNJ11*	Heterogeneous	No	Off medication
7	Day 3	39	3734	AGA	Developed side effect	Octreotide	Heterozygous mis sense mutation,*ABCC8*	Focal	Focal	Off medication
8	Day1	39	2900	AGA	Unresponsive	Octreotide	Heterozygous mis sense mutation, *ABCC8*	Focal	Focal	Off medication
9	Day 1	36	3280	AGA	Developed side effect	High carbohydrate	Heterozygous mutation, *KCNJ11*	Heterogeneous	No	Off medication
10	12 months	40	3600	AGA	Responsive		*Gain of function mutation, GLUD1*	No	No	On treatment
11	Day 3	40	3080	AGA	Responsive		Gain of function mutation, *GLUD1*	No	No	On treatment
12	Day 1	35	2580	AGA	Unresponsive	Octreotide	Heterozygous mis sense mutation, *ABCC8*	Focal	Near-total pancreatecto-my*	Diabetic

AGA appropriate for gestational age, *LGA* large for gestational age, *SGA* small for gestational age, *PEG* percutaneous endoscopic gastrostomy feeding

*All these patients had their operation before implementation of 18-fluro-Dopa PET CT and even before the recent advances in genetic analysis

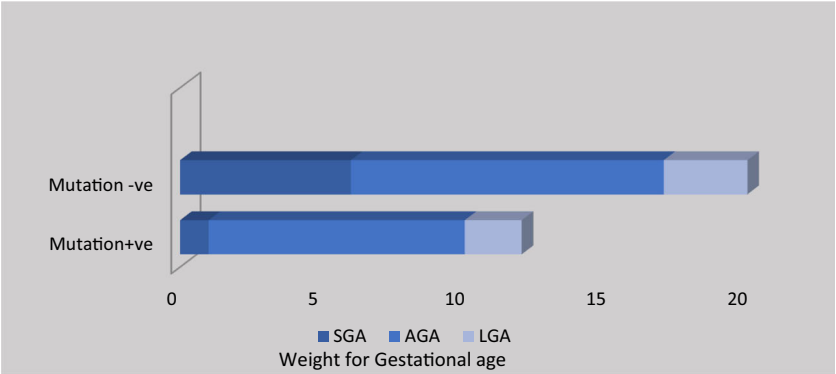

Fig. 2 Distribution of birth weight among patients with and without genetic mutations

spectrum disorders and one patient with *GLUD1* mutation had absence seizures and learning difficulties.

Discussion

Patients with CHI were almost all born at term and AGA. Patients with genetic mutations were mainly males (66.6%) and born AGA (75%) compared to 50% males and 55% AGA in those with no gene mutation. There was no significant difference in birth weight between both groups. As K-ATP mutations are the main genetic abnormalities in our cohort, these results are in contrast to another study which highlighted statistically significant increased birth weight and younger age of presentation in K-ATP mutation-positive group as compared to K-ATP mutation-negative patients [11]. This may be related to K-ATP mutations being mainly homozygous or compound heterozygous in the Turkish cohort.

In the current study, 37.5% had a genetically confirmed diagnosis in comparison to 45.3%, 51.4%, 66.7% and 79% respectively in four different studies [8, 11–13]. Mutations in the K-ATP channel genes were the commonest (75%) and were detected mainly in patients with diazoxide-unresponsiveness/diazoxide-related adverse effects.

In the set of patients who were diazoxide-responsive, no identifiable mutations in the known genes were found in 68.7% of patients, in comparison to 28% in an Iranian cohort of CHI [14], and 80% in a larger Italian cohort [12].

^{18}F-DOPA PET CT detected a focal lesion in all patients with paternally inherited *ABCC8* mutation. A focal lesion was also identified in one patient who was diazoxide unresponsive in the absence of an identifiable genetic mutation.

The three patients with paternally inherited mutations in *KCNJ11* had no focal lesions identified, however were still managed conservatively and off medication within the first year of life. This data supports previously reported data that a significant proportion, even as many as half, with paternal heterozygous K-ATP mutations may have diffuse CHI [15], and that resolution of CHI occurs in a significant proportion of those patients who were safely managed by conservative medical treatment [14, 16, 17].

Diazoxide-related circulatory side effects or cardiotoxicity were observed in 9.3% (3/32) of our patients in comparison to 41.9% in a recent report of Chinese patients (mainly oedema and fluid retention), suggesting the presence of different racial susceptibilities to diazoxide-related side effects [18].

Interestingly, 2/3 of paternally inherited *KCNJ11* mutation carriers initially responded to diazoxide, but then developed diazoxide-related cardiotoxicity, enforcing the fact that in cardiomyocytes, *Kir6.2* is integral in the make-up of myocellular K-ATP channel and that K-ATP channel malfunction has been implicated in the development and progression of heart disease [17]; however, with only 2 patients, we cannot make a definite conclusion.

Siblings with homozygous *KCNJ11* mutation were diazoxide unresponsive and had no cardiovascular side effects.

The introduction of ^{18}F-DOPA PET CT, together with advanced genetic studies, has been able to identify focal lesions more accurately, resulting in better surgical outcomes and should be also offered as early as indicated to avoid blind pancreatic resections and poor management outcomes [19].

Our results showed neurodevelopmental deficits in 19% of patients mainly autistic spectrum disorders and only one of them had an identified mutation (*GLUD1*, with associated absence seizures). There was wide variation in the reported neurodevelopmental deficits, from almost none in small series [20] to 44% in a larger cohort [21], and this may be related to sample size and phenotypical variability. Other studies reported the rate of psychomotor retardation to be more pronounced in neonatal onset versus infantile or later onset disease and also in the more severe forms of CHI [22, 23]. Most of our patients have no developmental delay, but those who do, learning difficulties are moderate to severe.

Conclusion

Although LGA and SGA are risk factors for CHI, most babies in our cohort were born AGA. Initial glucose requirement and insulin level at diagnosis do not influence the disease outcome. A genetic mutation does not exclude medical remission, with HH resolving in over 30% within the first 12 months of age; long-term conservative treatment of CHI is feasible as surgery sometimes does not guarantee complete remission, but it carries the risk of pancreatic dysfunction. The need for ongoing treatment in the absence of gene mutations suggests that there may be other novel genetic mechanisms involved in regulating insulin secretion. Early management of hypoglycaemia remains critical to prevent long-term neurological deficits.

Authors' Contributions Collection of Data: Khadiga Eltonbary, Guftar Shaikh

Manuscript Writing: Khadiga Eltonbary, Guftar Shaikh and Peter Robinson

Editing and Revision: Guftar Shaikh and Indi Banerjee

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Ethical approval for retrospective data collection by the Royal Hospital's ethical committee.

References

1. Rozenkova K, Guemes M, Shah P, Hussain K (2015) The diagnosis and management of hyperinsulinaemic hypoglycaemia. J Clin Res Pediatr Endocrinol. 7(2):86–97
2. Demirbilek H, Rahman SA, Buyukyilmaz GG, Hussain K (2017) Diagnosis and treatment of hyperinsulinaemic hypoglycaemia and its implications for paediatric endocrinology. Int J Pediatr Endocrinol. 2017:9
3. Arnoux JB, Verkarre V, Saint-Martin C, Montravers F, Brassier A, Valayannopoulos V et al (2011) Congenital hyperinsulinism: current trends in diagnosis and therapy. Orphanet J Rare Dis. 6:63
4. Galcheva S, Demirbilek H, Al-Khawaga S, Hussain K (2019) The genetic and molecular mechanisms of congenital hyperinsulinism. Front Endocrinol (Lausanne) 10:111
5. Bellanne-Chantelot C, Saint-Martin C, Ribeiro MJ, Vaury C, Verkarre V, Arnoux JB et al (2010) ABCC8 and KCNJ11 molecular spectrum of 109 patients with diazoxide-unresponsive congenital hyperinsulinism. J Med Genet. 47(11):752–759
6. Flanagan SE, Kapoor RR, Hussain K (2011) Genetics of congenital hyperinsulinemic hypoglycemia. Semin Pediatr Surg. 20(1):13–17
7. Senniappan S, Shanti B, James C, Hussain K (2012) Hyperinsulinaemic hypoglycaemia: genetic mechanisms, diagnosis and management. J Inherit Metab Dis. 35(4):589–601
8. Snider KE, Becker S, Boyajian L, Shyng SL, MacMullen C, Hughes N et al (2013) Genotype and phenotype correlations in 417 children with congenital hyperinsulinism. J Clin Endocrinol Metab. 98(2):E355–E363
9. Meintjes M, Endozo R, Dickson J, Erlandsson K, Hussain K, Townsend C et al (2013) 18F-DOPA PET and enhanced CT imaging for congenital hyperinsulinism: initial UK experience from a technologist's perspective. Nucl Med Commun. 34(6):601–608
10. Ismail D, Hussain K (2010) Role of 18F-DOPA PET/CT imaging in congenital hyperinsulinism. Rev. Endocr Metab Disord. 11(3):165–169
11. Demirbilek H, Arya VB, Ozbek MN, Akinci A, Dogan M, Demirel F et al (2014) Clinical characteristics and phenotype-genotype analysis in Turkish patients with congenital hyperinsulinism: predominance of recessive KATP channel mutations. Eur J Endocrinol. 170(6):885–892
12. Kapoor RR, Flanagan SE, Arya VB, Shield JP, Ellard S, Hussain K (2013) Clinical and molecular characterisation of 300 patients with congenital hyperinsulinism. Eur J Endocrinol. 168(4):557–564
13. Yorifuji T, Kawakita R, Nagai S, Sugimine A, Doi H, Nomura A et al (2011) Molecular and clinical analysis of Japanese patients with persistent congenital hyperinsulinism: predominance of paternally inherited monoallelic mutations in the KATP channel genes. J Clin Endocrinol Metab. 96(1):E141–E145
14. Senniappan S, Sadeghizadeh A, Flanagan SE, Ellard S, Hashemipour M, Hosseinzadeh M et al (2015) Genotype and phenotype correlations in Iranian patients with hyperinsulinaemic hypoglycaemia. BMC Res Notes. 8:350
15. Arya VB, Guemes M, Nessa A, Alam S, Shah P, Gilbert C et al (2014) Clinical and histological heterogeneity of congenital hyperinsulinism due to paternally inherited heterozygous ABCC8/KCNJ11 mutations. Eur J Endocrinol. 171(6):685–695
16. Salomon-Estebanez M, Flanagan SE, Ellard S, Rigby L, Bowden L, Mohamed Z et al (2016) Conservatively treated Congenital Hyperinsulinism (CHI) due to K-ATP channel gene mutations: reducing severity over time. Orphanet J Rare Dis. 11(1):163
17. Welters A, Lerch C, Kummer S, Marquard J, Salgin B, Mayatepek E et al (2015) Long-term medical treatment in congenital hyperinsulinism: a descriptive analysis in a large cohort of patients from different clinical centers. Orphanet J Rare Dis. 10:150
18. Ni J, Ge J, Zhang M, Hussain K, Guan Y, Cheng R et al (2019) Genotype and phenotype analysis of a cohort of patients with congenital hyperinsulinism based on DOPA-PET CT scanning. Eur J Pediatr. 178(8):1161–1169
19. Kurbet SB, Parameshwar Prashanth G, Patil VC (2013) Surgical management of congenital hyperinsulinism in a resource-limited setting. J Neonatal Surg 2(2):26
20. Dacou-Voutetakis C, Psychou F, Maniati-Christidis M (1998) Persistent hyperinsulinemic hypoglycemia of infancy: long-term results. J Pediatr Endocrinol Metab. 11(Suppl 1):131–141
21. Meissner T, Wendel U, Burgard P, Schaetzle S, Mayatepek E (2003) Long-term follow-up of 114 patients with congenital hyperinsulinism. Eur J Endocrinol. 149(1):43–51
22. Menni F, de Lonlay P, Sevin C, Touati G, Peigne C, Barbier V et al (2001) Neurologic outcomes of 90 neonates and infants with persistent hyperinsulinemic hypoglycemia. Pediatrics. 107(3):476–479
23. Kostopoulou E, Shah P (2019) Hyperinsulinaemic hypoglycaemia-an overview of a complex clinical condition. Eur J Pediatr. 178(8):1151–1160