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Original article

Clinical Characteristics and Long-Term Outcomes of Persistent Hyperinsulinemia Hypoglycemia of Infancy

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Abstract
Persistent Hyperinsulinemic Hypoglycaemia of Infancy (PHHI), also known as Congenital Hyperinsulinism (CHI), is the most common and severe cause of persistent hypoglycemia in neonates and infants. Delays in diagnosis can lead to permanent brain injury in up to 25–50% of cases. This study aims to describe the clinical characteristics, genetic findings, and long-term outcomes of PHHI patients in a Libyan tertiary center. We retrospectively reviewed 27 infants (17 males, 10 females) diagnosed with PHHI at Tripoli University Hospital between 1996 and 2024. Data regarding clinical presentation, birth history, consanguinity, biochemical markers (insulin, glucose, insulin-to-glucose ratio), genetic analysis, management, and long-term outcomes were analyzed. The mean birth weight was 4.0 kg, and the mean age of presentation was 3 weeks (range: 1 day to 6 years). High rates of consanguinity were observed (74%). Biochemical analysis showed mean insulin levels of 21.6 µU/ml during hypoglycemia, with an insulin-to-glucose ratio ranging from 0.75 to 8.0. Histologically, 7 patients (26%) had focal lesions, while 20 (74%) had diffuse disease. Twenty-four patients underwent sub-total or near-total pancreatectomy. Long-term complications included Diabetes Mellitus in 18 patients (66.6%) and unfavorable neurological outcomes in 3 patients due to late intervention. Neurologic and psychomotor retardation with ADHD was observed in 8 patients (29.6%), and epilepsy in 4 patients (14.8%). Genetic testing in 13 patients (48.1%) confirmed ABCC8 mutations in several cases. Conclusions: Early recognition and aggressive management are critical to preventing neurological damage in PHHI. Genetic studies are invaluable for determining the underlying cause and guiding surgical vs. medical management. In regions with high consanguinity, genetic counseling is essential for affected families.
Keywords: PHHI, Congenital Hyperinsulinism, Hypoglycemia, ABCC8, Pancreatectomy, Libya.

Introduction

Persistent Hyperinsulinemic Hypoglycaemia of Infancy (PHHI) is the most common and severe form of hyperinsulinemic hypoglycemia in neonates and infants. The risk of permanent brain injury in infants with HH continues to be as high as 25–50% due to delays in diagnosis and inadequate treatment. PHHI is a genetic disorder with familial and sporadic forms, both of which are characterized by dysregulation of insulin secretion occur in the neonates. Congenital hyperinsulinism (CHI) is caused by genetic mutations that disrupt insulin secretion regulation and primarily involves genes like ABCC8, KCNJ11, GLUD1, etc. [2].

A recent study described genetic abnormalities in nine genes (ABCC8, KCNJ11, GCK, SCHAD, GLUD1, SLC16A1, HNF1A, HNF4A, and UCP2) that lead to the congenital forms of HH (1,2). The most severe forms of CHH are due to defects in the genes (ABCC8 and KCNJ11) (3,4). The disease also shows histological variability, encompassing a diffuse form affecting the entire pancreas, a focal type called focal adenomatous hyperplasia, and isolated cases known as insulinomas [3].

In PHHI, the histological abnormalities in pancreatic structure are grouped into 2 categories. The first focal lesion has abnormal islet cells, the majority of focal CHH due to a heterozygous paternally inherited mutation in the ABCC8 or KCNJ11 gene, gene account for almost 30%–40% of all CHH cases. Focal CHH is usually confirmed by a fluorine-18 dihydroxyphenylalanine-positron emission tomography (18F-DOPA-PET) scan. Surgical resection of the lesion usually resolves HH .In diffuse PHHI, the PET scan shows uniform uptake of [18-F]-L-DOPA throughout the pancreas. In focal PHHI, the uptake of [18-F]-L-DOPA is concentrated within the foci of the disease. The second Diffuse CHH, the diffuse pancreas, affects all the pancreatic β-cells. Patients with diffuse CHH either have a homozygous recessive or a compound heterozygous mutation in their KATP channel genes. This form of CHH accounts for 60–70% of all CHH cases, require a near total pancreatectomy (5,6). Diagnosing hyperinsulinism (HI) hinges on obtaining a critical blood sample during spontaneous or provoked hypoglycemia, typically when plasma glucose is < 50 mg/dL (2.775 mmol/L). Key indicators also include a glucagon-stimulated rise in glucose.

Detectable insulin during hypoglycemia suggests inappropriate insulin secretion, though the absence of elevated insulin doesn't rule out HI as the diagnosis relies on a comprehensive assessment of biochemical markers rather than solely on insulin levels [4]. Lastly, the main objective of treatment is to avoid severe hypoglycemia and achieve blood glucose levels near normal. Treatment options encompass diet, pharmacotherapy modalities targeting insulin secretion, including diazoxide, octreotide, and glucagon, and surgery. A diet including frequent carbohydrate-rich meals is generally favored over pharmacotherapy, which in turn is preferred over surgical approaches depending upon the severity of the disease [7]

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Methods

We have reviewed 27 infants (17 male & 10 female) who presented with severe recurrent non-ketotic hypoglycaemia, insulin levels were (>10 µU/ml), and their Insulin-to-glucose rate was (> 0.3). In the period between 1996 and 2024, the mean age of presentation was 3 weeks (2 days- 3 months), except for one patient who was diagnosed at 6 years of age.
The diagnosis of the primary form of congenital hyperinsulinemic hypoglycaemia was confirmed by laboratory investigations. Analysis of data regarding the time & mode of presentation, birth history, family history, consanguinity, Initial blood sugar levels, Insulin levels, Insulin to glucose ratio, genetic analysis, management, histopathology & outcome of the patients was studied.

Results

A total of twenty-seven infants were enrolled in this retrospective analysis, comprising seventeen males and ten females, yielding a male-to-female ratio of 1.7:1. The mean birth weight was 4.0 ± 0.8 kg, ranging from 1.9 to 5.7 kg. The average age at presentation was three weeks, though the spectrum extended from the first day of life to six years, with one child presenting exceptionally late at six years of age. Consanguinity was strikingly prevalent, documented in twenty patients (74%), most often first-cousin unions. A family history of neonatal hypoglycemia was noted in three patients (11.1%), two of whom, along with one first cousin, were included in the present cohort.

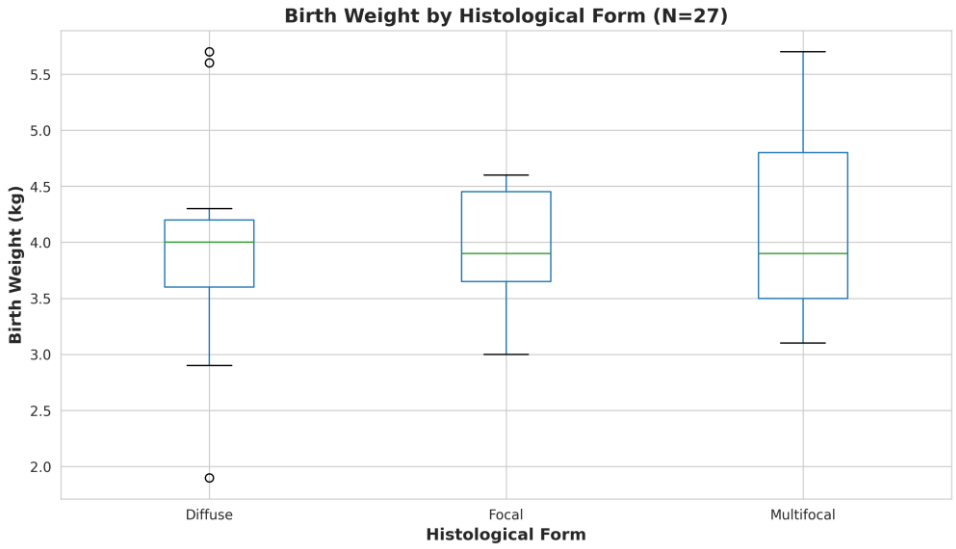

Figure 1: Birth Weight by Histological Form (N=27): examines the relationship between birth weight and histological form, indicating that focal lesions are often associated with larger birth weights compared to diffuse hyperplasia.

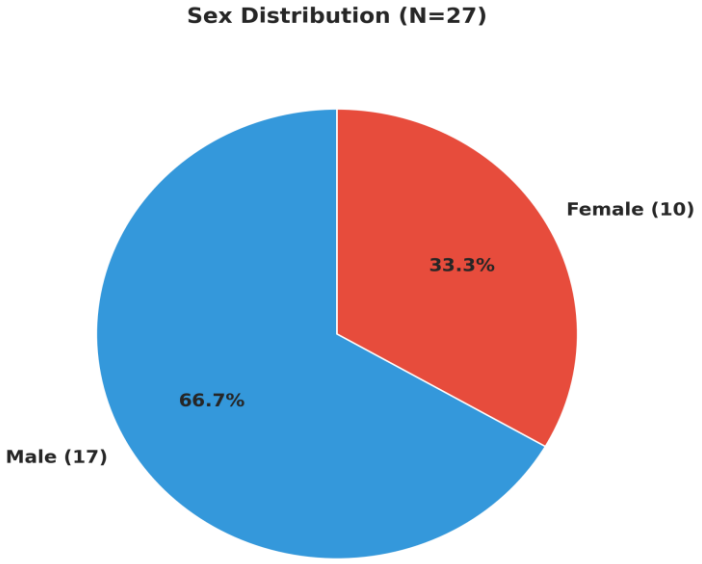

Figure 2: Gender Distribution (N=27) : illustrates the gender distribution within the study cohort, showing a male predominance with a male-to-female ratio of 1.7:1

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Initial biochemical evaluation revealed profoundly low glucose levels, ranging from 4 to 22 mg/dl, with a mean of 12 ± 5.2 mg/dl. Concurrent insulin concentrations during hypoglycemia averaged 21.6 ± 5.1 µU/ml (range: 16.6–32.0 µU/ml). The insulin-to-glucose ratio varied widely between 0.75 and 8.0, with a mean of 2.8 ± 1.9. Surgical intervention was required in twenty-four patients, who underwent sub-total to near-total pancreatectomy, while three patients were managed medically.

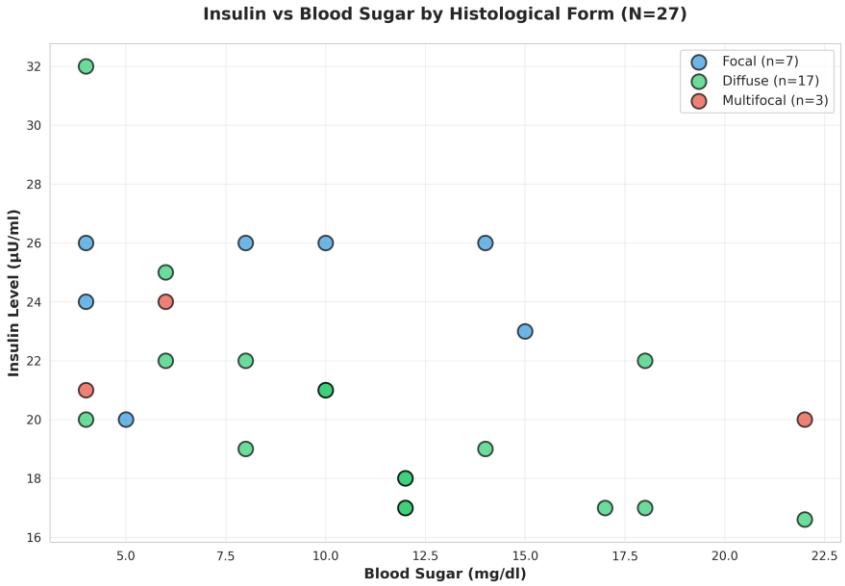

Figure 3: Insulin vs Blood Sugar by Histological Form (N=27) : compares insulin and blood sugar levels across the different histological forms, demonstrating the more severe biochemical profile typically associated with focal lesions.

Histopathological examination distinguished two forms of disease. The focal form was identified in seven patients (26%), characterized by insulin levels exceeding 20 µU/ml and blood glucose ≤12 mg/dl, with a sex distribution of four males and three females (ratio 1.3:1). The diffuse form was more common, affecting twenty patients (74%), associated with insulin levels ≤20 µU/ml and glucose >12 mg/dl, with a male predominance (15 males, 5 females; ratio 3:1). Overall, the male-to-female ratio across the cohort was 2:1. Clinically, large-sized infants tended to harbor focal lesions, whereas diffuse hyperplasia was more often observed in small or average-sized infants. The focal form proved more severe than the diffuse variant. Two male neonates presented within the first week of life with profound hypoglycemia (blood glucose 2–4 mg/dl) and elevated birth weights (4.5 and 5.7 kg). Their mothers had no history of gestational diabetes, and both infants were refractory to medical therapy. Surgical exploration revealed multifocal adenomatosis of the pancreas.

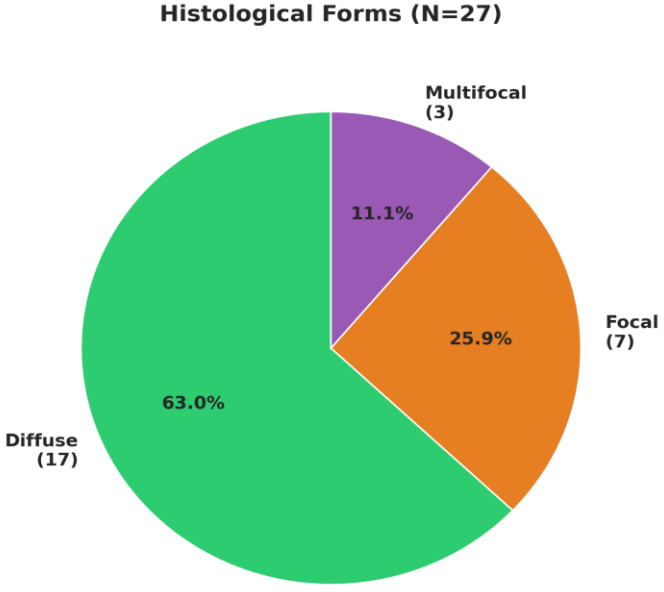

Figure 4: Histological Forms (N=27) : displays the proportion of focal versus diffuse histological forms of congenital hyperinsulinism observed in the patients, with the diffuse form being significantly more common.

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Long-term follow-up demonstrated that diabetes mellitus developed in eighteen patients (66.6%), including three with multifocal disease and the remainder with diffuse hyperplasia, with a mean age of onset of five years. Neurological sequelae were not uncommon: three patients (11.1%) suffered unfavorable outcomes due to delayed surgical intervention, while eight (29.6%) exhibited psychomotor retardation and attention-deficit hyperactivity disorder. Epilepsy was documented in four patients (14.8%). Mortality occurred in two cases (7.4%) during the study period.

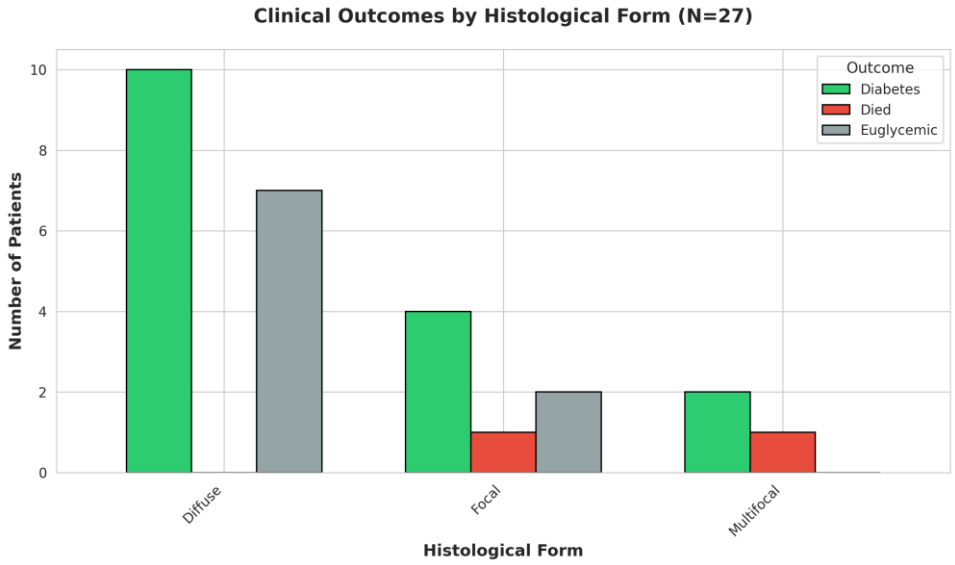

Figure 5: Clinical Outcomes by Histological Form (N=27): correlates the long-term clinical outcomes with the underlying histological form, showing the varying risk of complications such as diabetes depending on the disease subtype.

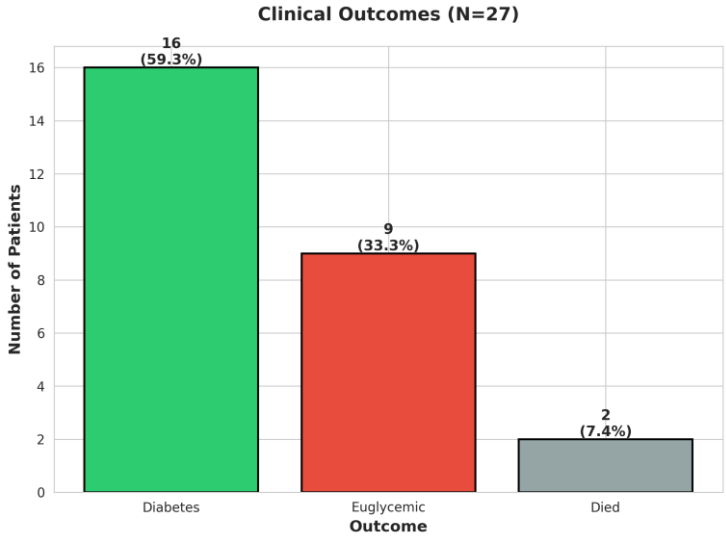

Figure 6: Clinical Outcomes (N=27) summarizes the long-term clinical outcomes of the cohort, highlighting the high incidence of diabetes mellitus and varying degrees of neurological impairment

Genetic analysis was performed in thirteen patients (48.1%). Homozygous mutations in the SUR (ABCC8) gene were identified in several cases, confirming autosomal recessive congenital hyperinsulinism. Heterozygous mutations in exon 3 of ABCC8 were also detected in specific patients. Overall, eight individuals (61.5% of those tested) were confirmed to harbor ABCC8 mutations, underscoring the genetic basis of the disorder within this cohort.

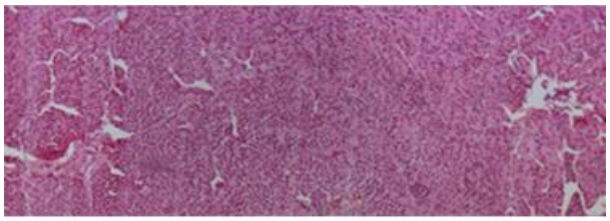

Figure 7. Histopathology demonstrates a well-demarcated focus of adenomatous B-cell hyperplasia; the lesion areas show dense clustering of endocrine cells occupying the majority of the affected lobules

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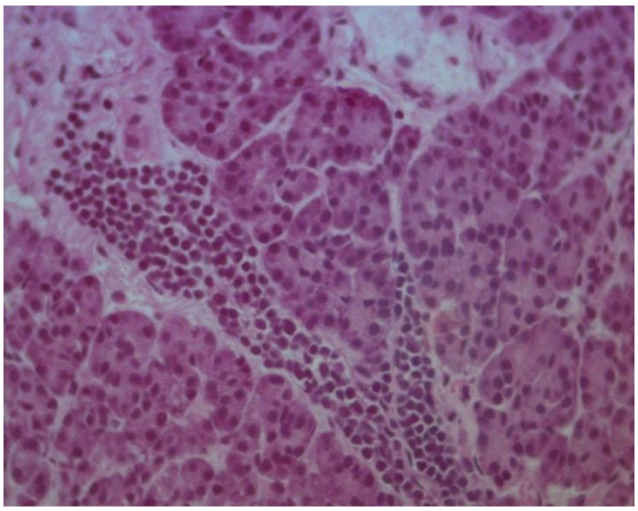

Figure 8. Histopathology diffuses: this specimen shows diffuse of pancreatic parenchyma with widespread hyperplastic endocrine cells distributed throughout the field. The B cells demonstrate marked hypertrophy with enlarged nuclei visible throughout the tissue

Table 1 provides a statistical summary of the clinical characteristics, biochemical markers, histopathological findings, and long-term outcomes of the 27 patients with congenital hyperinsulinism. The majority presented in the neonatal period with severe hypoglycemia and elevated insulin levels. The data highlights a predominance of diffuse disease, significant rates of long-term complications such as diabetes mellitus and neurological issues, and a high frequency of ABCC8 genetic mutations.

Surgical intervention was the predominant treatment, with most patients undergoing near-total pancreatectomy. Outcomes varied: while several achieved long-term euglycemia, a substantial proportion developed diabetes mellitus, particularly those with diffuse or multifocal disease. Neurological complications—including epilepsy, ADHD, and psychomotor retardation—were observed in a significant subset, often linked to delayed diagnosis or intervention. Mortality was documented in two patients. Genetic testing confirmed ABCC8 mutations in the majority of tested cases, underscoring the autosomal recessive inheritance pattern and highlighting the importance of genetic screening in clinical management and family counseling. The consistency of ABCC8 involvement across patients emphasizes its central role in disease pathogenesis.

Table 1. Clinical evaluation of patients with hypoglycemia–hyperinsulinism

Characteristic	**Value (n=27)**
Demographics	
Male: Female Ratio	1.7: 1 (17 males, 10 females)
Birth Weight (kg), Mean ± SD	4.03 ± 0.88
Birth Weight Range (kg)	1.9 - 5.7
Biochemical Markers	
Insulin Levels (μU/ml), Mean ± SD	20.76 ± 3.59
Blood Glucose (mg/dl), Mean ± SD	11.67 ± 5.47
Insulin-to-Glucose Ratio, Mean ± SD	2.43 ± 1.82
Histopathological Findings	
Diffuse	17 (63.0%)
Focal	7 (25.9%)
Multifocal	3 (11.1%)
Clinical Outcomes	
Diabetes	14 (51.9%)
Euglycemia	11 (40.7%)
Died	2 (7.4%)
Neurological Complications	
Normal	15 (55.6%)
ADHD	4 (14.8%)
Mental Retardation (MR)	2 (7.4%)
ADHD & Epilepsy	2 (7.4%)
MR & Epilepsy	2 (7.4%)
Genetic Testing (ABCC8)	
Positive	16 (59.3%)

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Discussion

This study represents one of the longest-running clinical reviews of PHHI in Libya, spanning nearly three decades. Our findings highlight several critical aspects of the disease in a North African context.

The high rate of consanguinity (74%) in our cohort is significantly higher than that reported in many Western studies. This underscores the importance of autosomal recessive inheritance in our population, particularly mutations in the ABCC8 and KCNJ11 genes. Similarly high rates of consanguinity have been reported in other Middle Eastern and North African cohorts, where the incidence of CHI is often higher than the global average of 1 in 50,000 live births.

The distribution of histological forms in our study (74% diffuse, 26% focal) is consistent with the higher prevalence of diffuse disease in populations with high consanguinity. Distinguishing between these forms is crucial, as focal disease can be cured by limited resection, whereas diffuse disease often requires extensive surgery with a high risk of subsequent diabetes. In our cohort, 22% of patients developed Diabetes Mellitus post-pancreatectomy, emphasizing the need for long-term endocrine follow-up.

The neurological outcomes in our study serve as a stark reminder of the severity of PHHI. The 25–50% risk of brain injury cited in literature was reflected in our cohort, particularly when surgical intervention was delayed. Early diagnosis and the availability of advanced imaging, such as 18F-DOPA-PET scans, are essential to improve these outcomes. While 18F-DOPA-PET was not available locally during the earlier years of this study, its integration into clinical practice is a priority for future management.

Genetic testing proved to be a vital tool for 13 of our patients. The identification of ABCC8 mutations, including a specific heterozygous mutation in Exon 3, aligns with global data pointing to K_{ATP} channel defects as the primary cause of severe CHI. Expanding genetic testing to all suspected cases will facilitate more personalized treatment plans and provide families with accurate genetic counseling.

The genetic landscape of CHI in our cohort aligns with broader findings in the Middle East and North Africa (MENA) region, where high rates of consanguinity significantly increase the prevalence of autosomal recessive conditions [10, 11]. Pathogenic variants in the ABCC8 and KCNJ11 genes, which encode the subunits of the pancreatic β-cell ATP-sensitive potassium (KATP) channel, remain the most common cause of severe, diazoxide-unresponsive hyperinsulinism [12]. The predominance of diffuse disease in our study is characteristic of recessive KATP channel mutations commonly seen in consanguineous populations.

Furthermore, the long-term complications observed, particularly the high incidence of post-pancreatectomy diabetes mellitus (66.6%), highlight a critical challenge in the management of diffuse CHI. While near-total pancreatectomy is often life-saving and necessary to prevent severe hypoglycemic brain injury, it invariably leads to pancreatic endocrine insufficiency over time. Recent studies have demonstrated that the cumulative incidence of insulin-dependent diabetes after extensive pancreatectomy for CHI can reach up to 91% by 14 years of age [13]. This underscores the need for continuous endocrinological monitoring and the potential benefits of exploring more conservative or targeted therapies when feasible.

The neurological outcomes in our cohort further emphasize the devastating impact of prolonged neuroglycopenia. Hypoglycemic brain injury in CHI is exacerbated by the hyperinsulinemic state, which suppresses the production of alternative brain fuels such as ketones and lactate [14]. This dual insult leads to a high risk of adverse neurodevelopmental outcomes, including psychomotor retardation and epilepsy, as seen in nearly a third of our patients.

The integration of advanced diagnostic modalities, such as 18F-DOPA-PET/CT imaging, has revolutionized the management of CHI by accurately differentiating between focal and diffuse forms and localizing focal lesions for curative partial pancreatectomy [15]. Although not universally available during the early years of this cohort, its adoption is imperative to improve surgical outcomes and minimize long-term squeal.

Conclusions

Early recognition, accurate diagnosis, and timely treatment are essential to prevent or minimize neurological damage in patients with congenital hyperinsulinism. Family education, together with long-term follow-up, plays a critical role in detecting recurrence and monitoring for the development of diabetes mellitus. Genetic studies are increasingly recognized as valuable tools, not only for identifying the underlying cause but also for guiding genetic counseling. Access to newer pharmacological agents and advanced imaging modalities, such as 18F-DOPA PET, has transformed management by enabling precise localization of focal lesions. This progress has made it possible to cure focal forms of persistent hyperinsulinemic hypoglycemia completely, thereby reducing the need for extensive surgical intervention. Careful preoperative investigations are crucial, as they help limit the extent of pancreatectomy and significantly reduce the risk of postoperative diabetes, ultimately improving long-term patient outcomes and quality of life.

Conflict of interest. Nil

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