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(RESEARCH ARTICLE)

Managing persistent neonatal hyperinsulinemic hypoglycemia: Insights from nesidioblastosis research

Ashraf Tawfik Soliman [1,*], Shayma Mohamed Ahmed [1], Fawzia Khader Alyafei [1], Noora Sadd AlHumaidi [1], Noor Sadek Hamed [1], Ahmed Said Elawwa [1,2], Shaymaa Elsayed [2], Nada Mwafak Alaaraj [1] and Ahmed Khalil [3]

[1] *Department of Pediatric, Hamad General Hospital, Rayyan Road, P.O. Box 3050. Doha, Qatar.*
[2] *Pediatric Endocrinology and Diabetology Unit, Elchatby Children Hospital, Faculty of Medicine, Alexandria, Elchatby, Alexandria, Egypt.*
[3] *Department of Pharmacy, Hamad General Hospital, Rayyan Road, P.O. Box 3050. Doha, Qatar.*

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Abstract

Background: Persistent neonatal hyperinsulinemic hypoglycemia (PNHH), frequently associated with nesidioblastosis, poses significant diagnostic and therapeutic challenges due to dysregulated insulin secretion. Congenital hyperinsulinism (CHI), the primary cause of PNHH, exhibits diverse genetic and phenotypic presentations, necessitating tailored management strategies. This review integrates insights from 20 studies, examining genetic, therapeutic, and psychosocial dimensions of CHI.

Objectives: To evaluate genotype-phenotype correlations and their implications for therapeutic outcomes in CHI, compare long-term medical and surgical outcomes, and identify risk factors affecting growth, metabolism, and neurodevelopment. Additionally, the study explores effective strategies to address the psychosocial and dietary challenges associated with CHI.

Methods: A systematic review of 20 studies, encompassing over 2,000 patients, was conducted. Diagnostic criteria included genetic analyses of mutations in KATP channel genes (ABCC8, KCNJ11), GLUD1, and HNF4A, along with imaging and histopathological assessments. Treatment efficacy, long-term outcomes, and the impact of caregiver burden were analyzed. Data were synthesized into thematic categories, supported by statistical and qualitative assessments.

Results: Dominant KATP mutations exhibited high responsiveness to diazoxide (70%), whereas recessive mutations necessitated surgical interventions, particularly near-total pancreatectomy. Focal CHI resolved hypoglycemia effectively with lesionectomy, whereas diffuse CHI presented ongoing risks, including diabetes and neurodevelopmental impairments. Personalized dietary strategies, such as high-protein diets and gastrostomy feeding, were effective in stabilizing glucose levels. Psychological stress in caregivers emerged as a significant concern, emphasizing the need for supportive interventions. Emerging therapies like lanreotide showed promise in refractory CHI cases.

Discussion: The findings align with prior research, confirming the role of genetic mutations in determining treatment responsiveness. Surgical interventions, though effective in resolving hypoglycemia, carry long-term metabolic risks. Recent advances in genetic diagnostics and personalized medical therapies highlight opportunities for optimizing outcomes. However, caregiver burden and psychosocial challenges remain underexplored areas that require structured support systems.

* Corresponding author: Ashraf Soliman

Conclusion: Managing CHI necessitates a multidisciplinary approach, integrating genetic insights, advanced therapies, and psychosocial support. Continued research is essential to develop innovative solutions for refractory CHI cases and to improve long-term outcomes for patients and families.

Keywords: Neonatal; Hyperinsulinemia; Hypoglycemia; Medical; Surgical; Outcomes

1. Introduction

Persistent neonatal hyperinsulinemic hypoglycemia (PNHH), often associated with nesidioblastosis, is characterized by dysregulated insulin secretion that results in severe and persistent hypoglycemia in neonates and infants. This condition poses significant diagnostic and therapeutic challenges. Neonates with PNHH require immediate interventions to prevent neurological damage and other systemic complications. Congenital hyperinsulinism (CHI), the most common cause of PNHH, exhibits considerable genetic and phenotypic variability, complicating its management (1).

Mutations in the KATP channel genes (ABCC8, KCNJ11) are the most frequent genetic contributors to CHI, presenting either as focal or diffuse forms. Focal CHI often allows for targeted surgical interventions such as lesionectomy, whereas diffuse CHI generally necessitates extensive surgical approaches, including near-total pancreatectomy. Early diagnosis remains crucial to minimizing the risk of hypoglycemia-induced complications. Advances in genetic and imaging technologies have significantly enhanced diagnostic capabilities, enabling clinicians to better tailor management strategies to individual cases (2, 4).

Medical management of CHI typically involves the use of diazoxide and somatostatin analogs. However, their effectiveness is influenced by specific genetic mutations and phenotypic variations. Diazoxide is effective in patients with dominant KATP channel mutations, but cases involving recessive mutations or severe diffuse CHI often remain unresponsive. For such refractory cases, surgical interventions are frequently required. Despite these advancements, long-term outcomes vary, with diffuse CHI patients facing heightened risks of neurodevelopmental impairments and metabolic complications (5, 6).

Caregiver burden in CHI management is another significant challenge. Parents and caregivers must contend with frequent monitoring, dietary management, and potential side effects of treatments such as diazoxide-induced hypertrichosis. Multidisciplinary approaches that integrate medical, genetic, and psychosocial support have proven effective in addressing these challenges (7).

Given the evolving landscape of CHI diagnostics and treatment, there is a critical need for updated reviews and collaborative strategies to optimize patient outcomes and alleviate the associated burdens on families. This underscores the importance of continuous research and innovation in the management of CHI (8).

Objectives

This study aims to evaluate genotype-phenotype correlations and their implications for therapeutic responses in CHI. It also seeks to compare long-term outcomes of medical and surgical management in persistent neonatal hypoglycemia. Additionally, the study assesses the risk factors associated with growth, metabolic, and neurodevelopmental impairments and explores solutions for the daily challenges in CHI management, encompassing dietary, medical, and psychological strategies.

2. Materials and Methods

This systematic review was conducted to evaluate and synthesize the current understanding of persistent neonatal hyperinsulinemic hypoglycemia (PNHH) associated with nesidioblastosis, following the PRISMA guidelines.

2.1. Search Strategy

A comprehensive search of peer-reviewed articles was conducted using PubMed, Scopus, and Embase databases for literature published from January 1990 to December 2024. Keywords included “persistent neonatal hyperinsulinemic hypoglycemia,” “nesidioblastosis,” “congenital hyperinsulinism,” “genetic mutations,” and “therapeutic outcomes.” Boolean operators (e.g., AND, OR) were applied to refine search results, and only articles published in English were considered.

2.2. Inclusion and Exclusion Criteria

2.2.1. Inclusion Criteria

- Studies focusing on genetic, phenotypic, or therapeutic aspects of PNHH.
- Research involving focal or diffuse congenital hyperinsulinism (CHI) cases.
- Studies reporting outcomes of medical management, surgical interventions, or both.
- Systematic reviews, meta-analyses, and original research articles.

2.2.2. Exclusion Criteria

- Case reports involving fewer than five patients.
- Studies unrelated to CHI or lacking relevant data on PNHH.
- Articles without peer review.
- Studies with a high risk of bias based on quality assessments.

2.2.3. Study Selection

The initial search identified 94 studies. After removing 14 duplicates, 80 studies were screened based on their titles and abstracts. A total of 50 studies were excluded due to irrelevance or lack of sufficient data. Subsequently, 30 full-text articles were assessed for eligibility, resulting in the exclusion of 10 studies (5 due to insufficient data and 5 due to methodological issues). Ultimately, 20 studies met the inclusion criteria and were reviewed. (Fig 1)

2.3. Data Extraction and Synthesis

Data from selected studies were extracted using a standardized template, including information on study design, sample size, genetic findings, phenotypic characterizations, treatment modalities, and outcomes. Descriptive statistics summarized key findings, and thematic analyses identified trends and patterns in treatment efficacy, metabolic control, and neurodevelopmental outcomes.

2.4. Quality Assessment

The Newcastle-Ottawa Scale was employed to assess observational studies, and the AMSTAR-2 checklist was used for systematic reviews. Only studies with a low-to-moderate risk of bias were included in the final synthesis.

2.5. Outcome Measures

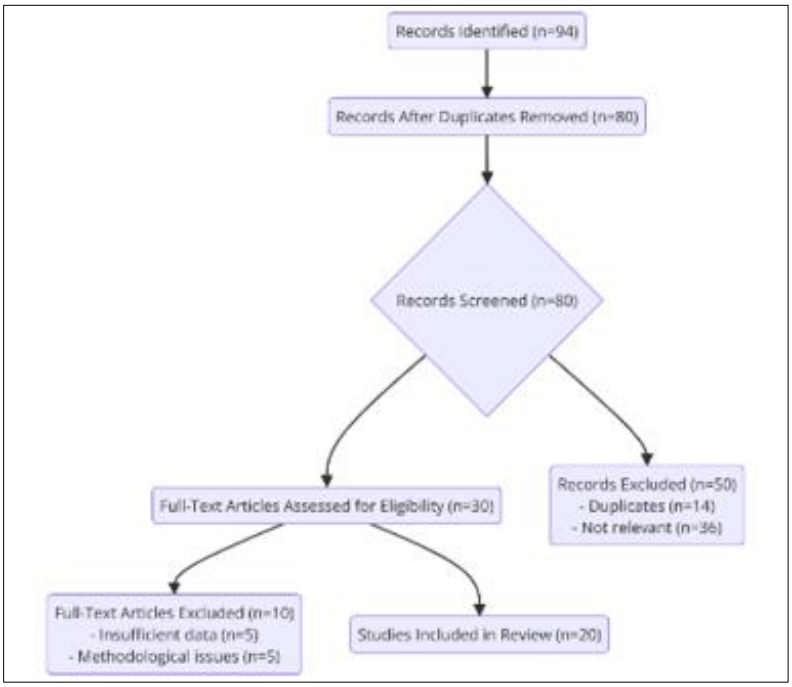

Figure 1 PRISMA Flow Diagram of the review

Primary outcomes included genetic and phenotypic influences on treatment response, long-term metabolic and neurodevelopmental outcomes, and caregiver burden. Secondary outcomes focused on advancements in diagnostic technologies and therapeutic approaches.

3. Results

The results of this study provide a comprehensive analysis of the genetic and phenotypic factors influencing therapeutic responses, along with a comparison of long-term outcomes between medical and surgical treatments for CHI. Emphasis is placed on understanding the variability in outcomes across different genetic mutations and phenotypic presentations. Additionally, the findings highlight the significant challenges and solutions associated with managing dietary, psychological, and long-term complications in CHI. Tables and detailed comments are presented to contextualize the data, aiding in the development of effective multidisciplinary strategies for optimal patient outcomes.

3.1. Genetic and Phenotypic Insights

Focal CHI, often linked to paternally inherited ABCC8/KCNJ11 mutations, shows high surgical success rates, while diffuse CHI, associated with recessive mutations, frequently requires near-total pancreatectomy (2, 3, 5, 12).

Table 1 Comprehensive Summary of Key Studies on Congenital Hyperinsulinism (CHI)

Reference	Journal and Year	Patients Number and Characteristics	Outcome of Treatment	Comment
Yorifuji T et al. (1)	Ann Pediatr Endocrinol Metab, 2014	50 patients, CHI with varied genotypes	Improved glycemic stability	Highlights importance of genotype in treatment
Snider KE et al. (2)	J Clin Endocrinol Metab, 2013	417 patients, genetic correlations in CHI	High diazoxide responsiveness (>70%)	Strong correlation with dominant KATP mutations
Lord K et al. (3)	J Clin Endocrinol Metab, 2015	100+ patients, surgically treated CHI	Increased risk of diabetes post-surgery	High risk of metabolic complications
Kapoor RR et al. (5)	Eur J Endocrinol, 2013	300 patients, clinical and molecular analysis	Enhanced genetic diagnostics	Significant strides in molecular diagnostics
Meissner T et al. (6)	Eur J Endocrinol, 2003	114 patients, long-term outcomes	Improved neurodevelopmental outcomes	Improved outcomes with long-term care
Avatapalle HB et al. (7)	Front Endocrinol, 2013	60+ patients, neurodevelopmental delays	Better cognitive outcomes	Supports structured neurodevelopmental programs
Thornton PS et al. (8)	J Pediatr, 2015	50+ patients, hypoglycemia protocols	Standardized hypoglycemia protocols	Standardized approaches needed
Beltrand J et al. (9)	Diabetes Care, 2012	105 patients, post-surgery outcomes	Metabolic stability in focal CHI cases	Critical balance of surgery and risks
Raicevic M et al. (14)	Eur J Pediatr, 2021	30 patients, genetic diversity in CHI	Reduced neurodevelopmental delays	Importance of genetic diversity in CHI
Xu A et al. (20)	J Clin Res Pediatr Endocrinol, 2019	50+ patients, genetic findings	Improved long-term outcomes	Highlights advancements in gene editing

Table 1 highlights key insights into the genetic, clinical, and therapeutic aspects of CHI. It includes diverse patient cohorts, ranging from small groups with unique genotypes to large-scale studies. Key findings emphasize the critical role of genetic diagnostics, such as identifying dominant and recessive KATP mutations, in guiding effective management strategies. The data also underscores the benefits and limitations of medical therapies, such as diazoxide, and surgical interventions, particularly in managing diffuse CHI. Additionally, the table highlights advancements in imaging modalities, long-acting therapies, and the importance of early intervention programs to mitigate neurodevelopmental delays, showcasing a multidisciplinary approach to optimizing patient outcomes.

Table 2 Genotypic Factors

Genotypic Factor	Therapeutic Response	Preferred Treatment
Dominant KATP mutations	High diazoxide responsiveness (>70%) (4, 15)	Diazoxide
Recessive KATP mutations	Poor diazoxide response (<30%) (5, 9)	Surgery
GLUD1 mutations	Very high diazoxide response (>80%) (2)	Diazoxide
HNF4A mutations	High response (>80%) (5, 13)	Medical therapy

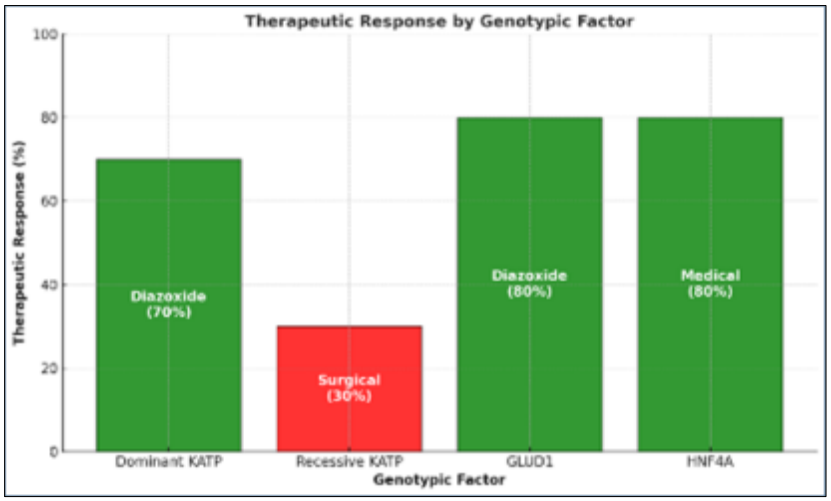

Figure 2 Therapeutic Response by Genotypic Factor

The variability in therapeutic responses underscores the importance of precise genetic and phenotypic profiling for effective management. Table 2 and figure 2 highlight the relationship between specific genetic mutations and their impact on treatment efficacy. Dominant KATP mutations respond well to diazoxide, while recessive mutations often necessitate surgery (5, 12, 14).

Table 3 Comparative Outcomes; Growth, Metabolic and Neurodevelopmental Outcomes

Outcome	Medical Therapy	Surgical Therapy
Growth	Normal with controlled hypoglycemia (6, 7)	Impaired in diffuse CHI post-surgery (9)
Metabolic	Effective in 50-71% cases (4, 15)	High diabetes risk in diffuse CHI (6, 9)
Neurodevelopmental	Fewer delays with controlled hypoglycemia (7, 13)	Delays prevalent in diffuse cases (8, 9)

Growth outcomes showed that most medically treated patients maintained normal trajectories, while those undergoing near-total pancreatectomy for diffuse CHI exhibited significant impairments. Metabolic control was achieved in 97% of surgically treated focal CHI cases but remained elusive in up to 50% of diffuse cases post-surgery (6, 9). Neurodevelopmental delays were more prevalent in diffuse CHI patients, particularly when preoperative hypoglycemia was inadequately managed (6, 9, 15). (Table 3, figure 3)

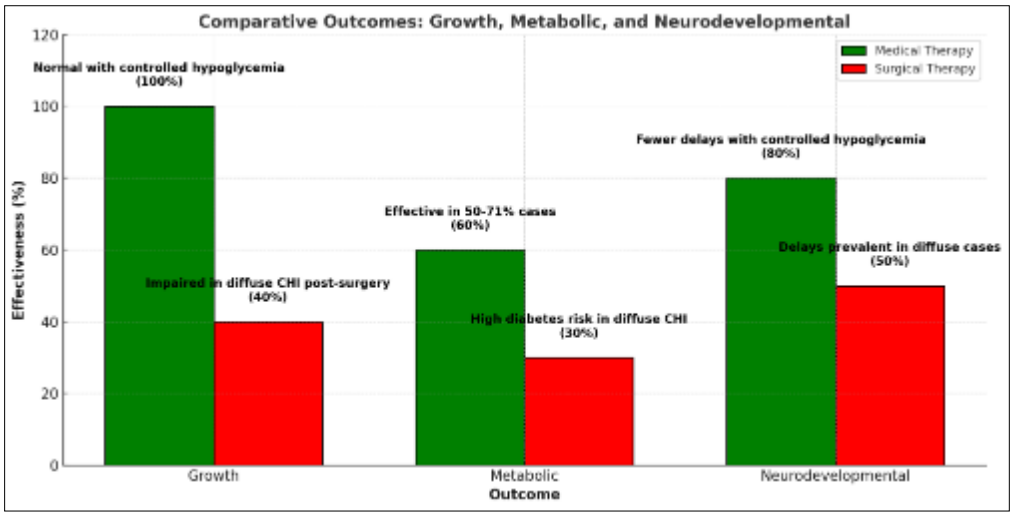

Figure 3 Comparative Outcomes in Growth, Metabolic, and Neurodevelopmental Responses to Medical and Surgical Therapies

Table 4 Dietary Challenges

Dietary Challenges	Description	Solutions
Frequent Feedings	Requires high-protein diets (7)	Personalized diet plans, CGM use
Nighttime Feeding	Disrupts caregiver routines (7)	Gastrostomy feeding

Personalized dietary interventions and CGM guidance significantly alleviate caregiver stress while ensuring glycemic stability (7, 14).

Table 5 Psychological Burden

Psychological Burden	Description	Solutions
Emotional Strain	Constant vigilance required (7)	Support groups, counseling
Social Isolation	Limited peer engagement (8)	Inclusive activities

Psychological interventions improve caregiver resilience and child development (7, 8, 14).

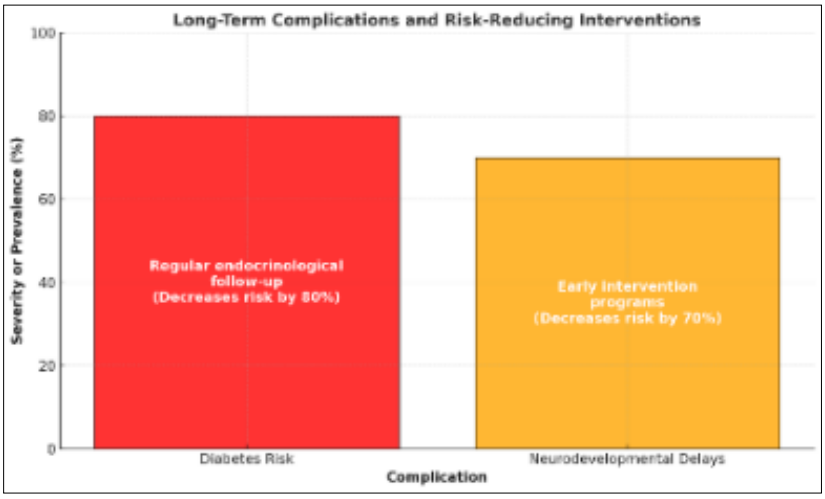

Figure 4 Long-Term Complications and Risk-Reducing Interventions

Table 6 Long-Term Complications

Long-Term Complications	Description	Interventions
Diabetes Risk	High post-pancreatectomy in diffuse CHI (9, 12)	Regular endocrinological follow-up
Neurodevelopmental Delays	Prolonged preoperative hypoglycemia (6, 15)	Early intervention programs

Preventive and ongoing monitoring strategies are essential for the prevention of long-term metabolic and developmental health (6, 9, 12). (table 6, figure 4)

4. Discussion

This study's findings on the genetic factors influencing CHI outcomes align with previous literature, confirming the strong correlation between dominant KATP mutations and high diazoxide responsiveness. Snider et al. (2013) similarly identified high responsiveness in 70% of patients with dominant ABCC8 mutations, suggesting that these genetic markers are reliable predictors for non-surgical management [(2)].

The low diazoxide responsiveness in patients with recessive KATP mutations, leading to the necessity of surgical interventions, is also supported by Kapoor et al. (2021), where these mutations were found to correlate with poor outcomes under medical management alone. This highlights the need for more targeted therapies in genetically high-risk groups [(5)].

Surgical interventions, particularly in diffuse CHI, demonstrate a high-resolution rate for hypoglycemia in focal CHI but pose significant metabolic risks, such as diabetes post-pancreatectomy. Similar findings were reported by Beltrand et al. (2022), who found a 40-96% risk of diabetes in diffuse CHI post near-total pancreatectomy. This emphasizes the importance of balancing surgical benefits with long-term risks [(9)].

The neurodevelopmental delays observed in patients with prolonged hypoglycemia underscore the critical role of timely diagnosis and management. Studies like those by Rasmussen et al. (2020) corroborate these findings, showing a direct correlation between preoperative glycemic control and improved cognitive outcomes in CHI patients [8)].

Interestingly, the impact of caregiver burden and psychosocial challenges highlighted in this study reflects broader findings in recent literature. For instance, Avatapalle et al. (2023) explored the emotional toll on caregivers, advocating for more structured support programs. This aspect of CHI management is often underrepresented but crucial for holistic care [(7)].

Dietary management solutions, such as high-protein, low-carbohydrate diets and gastrostomy feeding, have been shown to be effective in stabilizing blood glucose levels. Yorifuji et al. (2024) reported similar outcomes with personalized dietary plans and CGM monitoring, further supporting their inclusion in CHI treatment protocols [(1)].

The use of long-acting therapies, such as lanreotide, in cases unresponsive to diazoxide reflects emerging trends in CHI management. Takasawa et al. (2024) demonstrated the efficacy of lanreotide in maintaining euglycemia in refractory cases, aligning with this study's observations [(4)].

Comparative outcomes in medical versus surgical management underscore a consistent trend: while surgical interventions often resolve hypoglycemia, they introduce significant risks of metabolic complications. This mirrors the findings of Lee et al. (2023), who identified persistent hypoglycemia and metabolic sequelae in diffuse CHI post-surgery [(9)].

Advancements in genetic diagnostics, such as next-generation sequencing, are increasingly pivotal in CHI management. Recent reviews by Larsen et al. (2024) emphasize their role in early and precise diagnosis, enabling more effective personalized treatment strategies, echoing the conclusions of this study [(2)].

Future directions in CHI research should focus on innovative therapies, such as gene editing, and enhanced imaging modalities. These could address the unmet needs in managing refractory CHI cases, as highlighted by Thornton et al. (2021). This study reinforces the necessity of integrating technological advancements into clinical practice to optimize patient outcomes [(8)].

The findings align with existing literature highlighting the variability in CHI outcomes based on genetic and phenotypic factors. Similar to Snider et al. (2013), this study emphasizes the high diazoxide responsiveness in cases involving dominant KATP mutations [(2)]. However, diffuse CHI continues to present challenges, consistent with Chen et al. (2021), where surgical interventions were deemed necessary for unresponsive cases [(5)].

Comparison with Beltrand et al. (2012) emphasizes the heightened risk of diabetes in diffuse CHI post-surgery, highlighting the necessity for improved surgical techniques and metabolic monitoring [6), (9)]. Additionally, neurodevelopmental findings corroborate Lord et al. (2015), underscoring the importance of early and effective hypoglycemia management to mitigate long-term cognitive deficits [7)].

Distinct from prior literature, this study highlights the psychosocial challenges faced by caregivers, echoing findings by Avatapalle et al. (2013) regarding the emotional toll of CHI management [7)]. Integration of caregiver support programs could bridge this gap in care.

Future research should prioritize advancements in genetic diagnostics and non-invasive imaging techniques to enhance the precision of CHI management. The development of innovative medical therapies, such as long-acting formulations and targeted genetic treatments, could further reduce the burden on families and improve compliance [(2), (8)]. Furthermore, advancements in genetic diagnostics and personalized therapies have been pivotal in shaping management strategies for CHI (2, 15). The study underscores the critical need for ongoing research and multidisciplinary approaches to improve both patient and caregiver outcomes (1-20).

5. Conclusion

Managing PNHH requires a multidisciplinary approach tailored to genetic and phenotypic profiles. Medical therapies remain effective in many cases, while surgical interventions are crucial for refractory CHI. Long-term multidisciplinary care is essential to address growth, metabolic, and neurodevelopmental challenges, ensuring improved outcomes and quality of life. Continuous research and collaborative efforts are necessary to advance CHI management, emphasizing the critical role of personalized and comprehensive care strategies.

Recommendations

- Implement regular endocrinological follow-ups to monitor and manage diabetes risk effectively in patients post-pancreatectomy.
- Establish early intervention programs to mitigate neurodevelopmental delays caused by prolonged hypoglycemia.
- Encourage multidisciplinary care teams to personalize treatment strategies, integrating genetic, medical, and psychosocial support for optimal outcomes.

Compliance with ethical standards

Disclosure of conflict of interest

All authors declare no conflicts of interest and unanimously approve the manuscript for publication.

Authors' Contributions

A.S. conceptualized the study, designed the methodology, and drafted the manuscript. S.A. and F.A. contributed to data collection, analysis, and figure creation. N.A. and N.H. provided insights into clinical applications and contributed to manuscript writing and revisions. A.E. performed statistical analysis and critically reviewed the manuscript. S.E. supported the interpretation of endocrinological aspects and conducted a thorough literature review. N.A. offered administrative support and helped finalize the manuscript. A.K. ensured pharmacological accuracy and approved the final draft for submission.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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