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Etiology and outcome of hypoglycemia in young children: A retrospective cohort study

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ABSTRACT

Objectives: Hypoglycemia is one of the most common presenting complaints at a pediatric emergency department. There are many distinct causes of hypoglycemia, ranging from nutritional insufficiency to infectious origins to metabolic disorders. Full clinical assessment and appropriate investigations can help differentiate the cause of hypoglycemia with subsequent tailored management. All patients with hypoglycemia should have a full clinical assessment together with a hypoglycemia screen if appropriate. This clinical review aims to determine the investigation of hypoglycemia in young children (<6 years) and whether these patients received a subsequent diagnosis and adequate follow-up plans.

Material and Methods: The laboratory database searched for all children from 0 to 6 years old, with hypoglycemia defined as plasma glucose (PG) <54.0 mg/dL (or <3.0 mmol/L) from 2013 to 2021 at the Royal Hospital of Children, Glasgow. Cases were reviewed for the biochemistry investigations to determine if they had hypoglycemia screening requested and/or performed the presenting complaint, clinical diagnosis, and subsequent follow-up arrangements.

Results: Five hundred and one children were identified with hypoglycemia (PG <54.0 mg/dL) over a 9-year period. Of these patients, 28% (142/501) had a full hypoglycemia screen, 38% had a partial screen, and 34% (166/501) had no additional blood tests related to hypoglycemia screening other than a PG. The cause of hypoglycemia was identified in 15% (77/501), with gastroenteritis being the most common cause. Of those who were hypoglycemic, 48% (240/501) had an ongoing follow-up. Among those with severe hypoglycemia (PG ≤27.0 mg/dL) (86/501), causes were identified in 72% (62/86) and 63% (54/86) of this cohort which was followed up after the first presentation.

Conclusion: Screening was not consistently performed for all patients presenting with hypoglycemia. A great portion of patients were not fully investigated or followed up. This could be a result of clinical judgment in the assessment of further investigation for hypoglycemia. However, moderate and severe hypoglycemia still require further investigations, which can potentially lead to long-term consequences if not managed appropriately.

Keywords: Hypoglycaemia, Children, Outcome

INTRODUCTION

Hypoglycemia is one of the most common pediatric emergencies presented at the emergency department. Recognizing the clinical signs and symptoms and appropriate management are essential to prevent unwanted long-term neurological complications and death. Investigations should also be performed in a timely and appropriate manner to identify the cause of hypoglycemia and prevent future episodes. Common causes of hypoglycaemia in children include infection causes and metabolic disorders.

Table 1: Summary of the total cases, diagnosis, and follow-up rate in different degrees of hypoglycemia.

Degree of hypoglycemia (mg/dL)	Total cases	Investigation (full/partial/none) (%)	Diagnosis reached (%)	Follow up (%)
53.9–45.1	193	47 (24)/69 (36)/76 (39)	136 (70)	86 (45)
45.0–27.1	222	65 (29)/85 (38)/73 (33)	170 (77)	99 (45)
≤27.0	86	30 (35)/39 (45)/17 (20)	62 (72)	54 (63)

The definition of hypoglycemia remains controversial, especially in the newborn period, with thresholds ranging from plasma glucose (PG) <46.8–54 mg/dL.[1-3] Investigations for hypoglycemia also vary across hospitals; each of them has its unique guidelines with specific blood tests (the hyposcreen, definitions will be specified in 'patients and method' section) to order and subsequent management.[4] Besides the routine blood tests such as full blood count, liver function test, urea and electrolytes, and C-reactive protein, there are certain overlaps among these guidelines: PG, insulin/C-peptide levels, beta-hydroxybutyrate, non-esterified fatty acid (NEFA), cortisol, and lactate samples should be obtained before administration of glucose. Additional tests, such as ammonia, growth hormone, thyroid function tests, plasma amino acids, and acylcarnitine profile, can be done after the administration of glucose.

In the hyposcreen, laboratory glucose should be the priority as it confirms the state of hypoglycemia, and point-of-care testing is not always accurate, especially at lower glucose levels.[3,5]

Although the link between transient episodes of hypoglycemia and brain development remains unclear, studies have proven that prolonged episodes of hypoglycemia can directly lead to cerebral damage.[6] Long-lasting adverse effects on motor and cognitive neurological functions are associated with untreated or delayed treatment of neonatal hypoglycemia in preschool children. These complications may not be apparent at the neonatal stage, suggesting the need for long-term follow-up until school age.[7,8]

Due to the urgency of addressing immediate correction of hypoglycemia in children to prevent long-term consequences, investigations into the underlying cause of low glucose levels are often overlooked in initial management. However, investigations are important in determining the etiology of hypoglycemia, especially in the cases of recurrent and severe hypoglycemia, to exclude underlying metabolic and congenital hyperinsulinism.[4] This study aims to determine the investigation of hypoglycemia in young children (≤6 years), followed by the cause of hypoglycemia, and whether a clear subsequent diagnosis was made with appropriate follow-up.

MATERIAL AND METHODS

Patients aged up to 6 years who had an episode of PG level <54.0 mg/dL (<3.0 mmol/L) were searched for in the Royal Hospital for Children, Glasgow laboratory databases over the nine years (2013–2021). No diabetic patients were included in the initial search. After excluding 95 patients undergoing insulin tolerance tests, a total of 555 samples of PG <54.0 mg/dL were identified. After excluding the 54 duplicate samples, 501 patients remained in the cohort [Figure 1] for a summary of the patient groups.

In this study, hypoglycemia was classified into three groups: mild (53.9–45.1 mg/dL), moderate (45.0–27.1 mg/dL), and severe (≤27.0 mg/dL). The electronic clinical records documented all the biochemistry investigations the patients underwent during their admission. The results of PG, insulin or C-peptide, beta-hydroxybutyrate, NEFA, cortisol, and lactate were reviewed to determine if the patient received a full hyposcreen. A full hyposcreen is defined as obtaining a record of plasma glucose (PG), insulin or C-peptide, beta-hydroxybutyrate, and NEFA values. A partial screen was defined as having a PG value and any of the insulin, C-peptide, beta-hydroxybutyrate, NEFA, lactate, cortisol, and ammonia values. All biochemistry tests were performed on the Abbot Architect Ci1600/i2000SR analyzers. The presenting complaint, diagnosis, clinical outcomes, and follow-up plans were also noted in the discharge and clinical letters.

Statistics

A chi-square test was implemented to determine the statistical significance between gender/age and the incidence of hypoglycemia. The summary statistics are compiled in tables and pie charts [Tables 1 and 2; Figures 1-3]. Continuous variables are described as median and ranges, and inter-group comparisons are performed by Students' t-tests. Statistical significance was considered when $P < 0.05$. All analyses were conducted using GraphPad Prism 9.4.0.

This is a retrospective cohort study aiming to recognize the total incidence, investigations, etiology, and outcomes of pediatric hypoglycemia. Ethical approval was not required as this study was part of a health service evaluation.

RESULTS

Descriptive analysis

A total of 501 patients were included in this study, of which 287 were male, and 239 patients were <1 year old. The median

Table 2: Summary of total neonatal cases, diagnosis, and follow-up rate in different degrees of hypoglycemia.

Degree of hypoglycemia (mg/dL)	Total neonatal cases	Investigation (full/partial/none) (%)	Diagnosis reached (%)	Follow up (%)
53.9–45.1	44	10 (22)/17 (39)/17 (39)	31 (70)	22 (50)
45.0–27.1	87	21 (24)/36 (41)/30 (34)	67 (77)	48 (55)
≤27.0	51	17 (33)/29 (57)/5 (10)	45 (88)	32 (63)

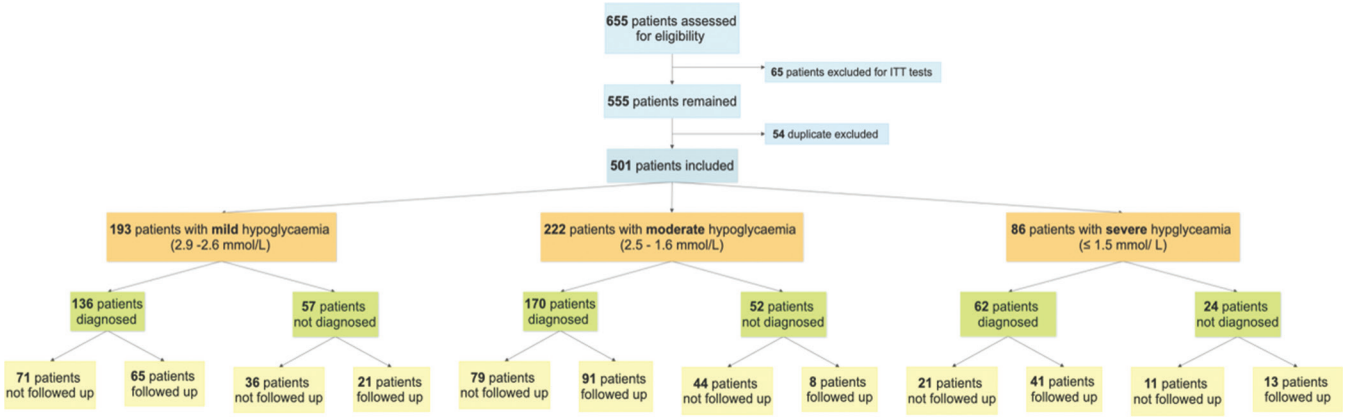

Figure 1: Consort diagram of the total patient cohort, subgrouping into mild, moderate, and severe hypoglycemia and their diagnosis and follow-up status, ITT: Insulin tolerance test.

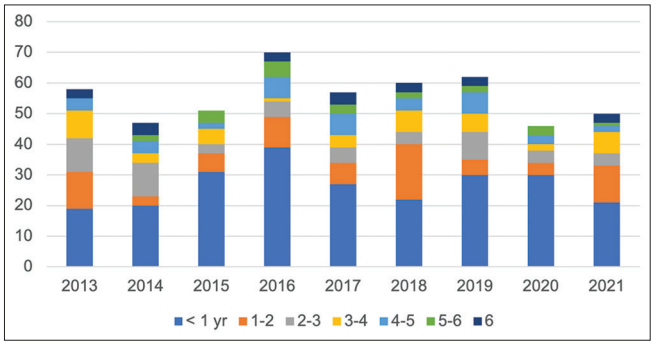

Figure 2: Age distribution and incidence of hypoglycemia from 2013 to 2021.

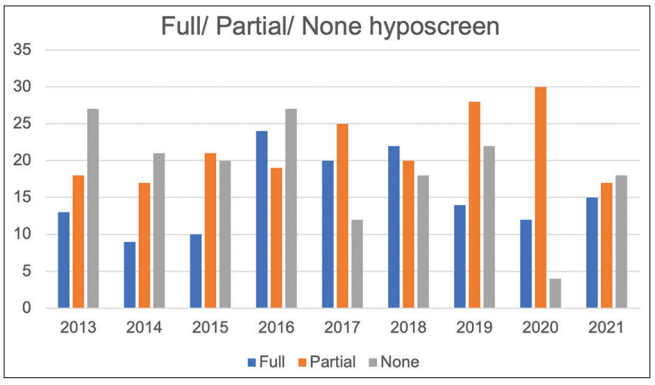

Figure 3: Completeness of hyposcreen each year from 2013 to 2021.

age of the patients was 1.5 years, with a range of 0–6 years. There was no statistically significant difference in age among males and females. However, there was a strong correlation between age and hypoglycemia. The data showed that the majority of the patients were <1 year of age ($P < 0.01$).

Completeness of investigations

Overall, 29% (142/501) of the entire group had a full hyposcreen, 38% (193/501) had a partial screen, and 33% (166/501) had no screening at all. There was a higher trend that more partial/full screenings have been done in more recent years. Figure 3 shows the trend of partial/full screenings done each year. The severe hypoglycemia group had the highest full/partial screening rate compared to the other two groups; however, 20% (17/86) of the severely hypoglycemic patients had no investigations at all.

Degree of hypoglycemia

The degree of hypoglycemia was separated into three groups: Mild, moderate, and severe hypoglycemia. One hundred and ninety-three cases (39%, 193/501) were identified as mild hypoglycemia, followed by 222 cases (44%) as moderate hypoglycemia, and 86 cases (17%) as severe hypoglycemic of which 39 patients (45%, 39/86) were neonates (age <1 year). Within each group, the percentage of cases that were given a diagnosis was similar to 70%, 77%, and 72% in the order of mild, moderate, and severe hypoglycemia. However, most patients were not followed up, with only 45% of patients

Table 3: Reported causes of hypoglycemia.

Primary diagnosis	Cases (%)
Unknown	133 (26.5)
Neonatal hypoglycemia	86 (17.2)
Gastroenteritis	79 (15.8)
Congenital hyperinsulinism	29 (5.8)
Ketotic hypoglycemia	27 (5.4)
Respiratory tract infection	23 (4.6)
Sepsis	21 (4.2)
Gastro-related cause	18 (3.6)
Hematology-related cause	17 (3.4)
Cardio-related cause	16 (3.2)
Renal-related cause	14 (2.8)
Metabolic cause	10 (2)
Urinary tract infection	9 (1.8)
Oncology-related cause	8 (1.6)
Meningitis	7 (1.4)
Respiratory-related cause	5 (1)

followed up in both mild and moderate hypoglycemia groups (86 cases with the mild hypoglycemia group and 99 patients with moderate hypoglycemia.) Despite having the highest follow-up rate out of the three groups, there were still 37% (32/86) of cases with severe hypoglycemia that had no follow-up plans.

Neonatal hypoglycemia

A total of 182 neonates were identified, aged <28 days of age, comprising 57 females and 125 males. The age range varied from 0 to 25 days, with a median age of 1 day. Forty-four of these 182 neonates (24%) had mild hypoglycemia, 87 (48%) had moderate, and 51 (28%) were categorized as severely hypoglycemic. The proportion of cases that received a diagnosis was approximately 70%, 77%, and 88% for mild, moderate, and severe hypoglycemia, respectively. More than half of the patients received follow-up care (102/182, 56%) regardless of the degree of hypoglycemia. Among the severely hypoglycemic neonates, the diagnostic rate was the highest at 88% (45/51), along with the highest follow-up rate at 63% (32/51).

Efficacy of the screening

Many insulin and C-peptide samples were found to be hemolyzed or insufficient. Of the 227 insulin samples collected for the hyposcreen, 63 (20%) samples were hemolyzed, and 22 (7%) samples were insufficient. On the other hand, 174 C-peptide samples were collected. Only 3 (1%) samples were hemolyzed and 20 (8%) samples were insufficient.

Presenting complaints and diagnosis

The diagnoses of hypoglycaemia for the 501 patients in this study are compiled in Table 3. The most common presenting complaint was vomiting with or without diarrhea (22.5%), which was consistent with the second most common primary diagnosis of gastroenteritis, followed by poor oral intake. In the neonatal age group, 86 patients (86/182, 47%) were given a diagnosis of neonatal hypoglycemia, 15 patients were diagnosed with hyperinsulinism (15/182, 8%), and two patients had glycogen storage disorder.

Recurrent hypoglycemia

Eight cases were identified with more than one episode of hypoglycemia, occurring between the ages of 5 weeks–6 years. Their PG ranged between 27.1 and 53.0 mg/dL, falling within the mild-to-moderate group. All children exhibited symptomatic hypoglycemia, characterized by symptoms such as vomiting, poor/reduced oral intake, lethargy, and unresponsiveness, and in two cases, hypoglycemic seizures were reported.

Subsequently, five patients received definitive diagnoses following comprehensive biochemical and genetic assessments, while six cases were monitored regularly within the endocrine and metabolic service. Among the diagnosed cases, two patients were diagnosed with idiopathic hypoglycemia, one patient with recurrent gastroenteritis and colitis of unspecified origin, and an additional two were diagnosed with hyperinsulinism. A patient exhibiting recurrent hypoglycemia-induced seizure was referred to neurology for further investigation and management. Only one patient out of the eight had a full screen after the first presentation. Six patients had a partial screen to investigate the cause of the persistent hypoglycemia, but one patient was discharged without further investigation and a follow-up plan.

DISCUSSION

The result of this study shows that 67% of patients presenting with hypoglycemia had some form of further investigations other than PG performed. Given that a number of patients presented with vomiting and/or diarrhea, it is most likely that the clinical judgment was used to manage the symptoms before running extensive investigations, as their hypoglycemia was most likely to be secondary to an underlying infection. However, for those patients who presented with additional symptoms such as lethargy, decreased appetite, unresponsiveness, and seizures, a full hyposcreen should be performed to exclude other underlying causes, especially as endocrine and metabolic pathologies can be potentially missed if a full screening is not performed at the time of hypoglycemia. Management and, in particular, investigations of hypoglycemia in childhood remain variable. While there have been improvements in performing hyposcreens over the years due to the use of readily available hypopacks, this remains suboptimal. To increase the utilization of hypopacks, regular educational

sessions should be conducted for both general pediatricians and emergency medicine staff, emphasizing the significance of timely investigations for episodes of hypoglycemia.

The demographic profile of the neonatal-specific subgroup closely mirrors that of the overall cohort, with a slightly elevated prevalence of severe hypoglycemic cases. On further comparison between the neonatal-specific subgroup and the entire cohort, there are no evident disparities in investigative, diagnostic, and follow-up within the mild and moderate hypoglycemia groups. However, a discernibly higher proportion of patients in the severe hypoglycemia category received diagnoses and underwent subsequent follow-up. This observation may be attributed to the indeterminate pathophysiological underpinnings of neonatal hypoglycemia. Maintaining optimal PG levels plays a pivotal role in early-stage development, thereby necessitating heightened vigilance and more frequent follow-up measures.

The etiology of hypoglycemia also remains unclear, as evidenced by an unknown diagnosis for 27.7% of all cases. This uncertainty arises from the imperative clinical decision to promptly correct the PG levels, often resulting in incomplete investigation. Notably, instances of recurrent hypoglycemia were received through thorough monitoring in clinics, and a diagnosis was given after extensive investigations in select cases. Even among the reported diagnoses, 16.8% were attributed to neonatal hypoglycemia, and 5.2% were classified as ketotic hypoglycemia. It is important to underscore that both ketotic and neonatal hypoglycemia are descriptive rather than definitive diagnoses, which ideally require further investigations to be performed. Not all patients who were diagnosed with ketotic hypoglycemia underwent a complete investigation: 35% had a full hyposcreen, and 65% had a partial screen. About 90% of the patients diagnosed with neonatal hypoglycemia were investigated, leaving 10% with no investigative measures at all.

A number of patients with severe hypoglycemia (20%) did not have any investigations performed, and 36% were not followed up after discharge. The severely hypoglycemic patient should still be followed up to ensure that there is no underlying cause that can be identified and also to exclude potential long-term complications as a result of the hypoglycemia.

A weakness of this study is that this is a retrospective study, primarily looking at the presentation, investigation, and follow-up rate of the children presented with hypoglycemia. As mentioned earlier, clinical judgment at presentation can determine the plan for management of hypoglycemia. Further, investigations may not be deemed necessary if the patient is clinically well.

CONCLUSION

The screening process for children presenting with hypoglycemia lacks consistency, leading to a significant portion of cases being inadequately investigated and left without proper follow-up. This trend may stem from the exercise of clinical judgment when assessing the need for further investigation, particularly in the cases of mild hypoglycemia.

This retrospective study underscores the suboptimal nature of investigations for hypoglycemia in childhood. While there has been an increase in the rate of hypoglycemia investigations over the years, with two-thirds of the patients now screened, it still falls short of the ideal standard as a significant number of cases remain without a clear diagnosis or subsequent follow-up plan.

The gravity of hypoglycemia, especially when severe, cannot be overstated. It demands appropriate investigation to identify underlying causes whenever possible to prevent the risk of recurrent hypoglycemic episodes and potential long-term neurological developmental insult.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent is not required as patient's identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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