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Idiopathic Pathological Ketotic Hypoglycemia: Finding the Needle in a Haystack

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Abstract
Sick children often have a decreased appetite and experience vomiting and diarrhea; however, hypoglycemia (plasma glucose concentration ≤50 mg/dL or 2.8 mmol/L) is rare. Ketotic hypoglycemia (KH) is the most common cause of hypoglycemia presenting to an Emergency Department in a previously healthy child between 6 months and 6 years of age. Ketosis and hypoglycemia are now well understood to be normal physiologic responses of young children to prolonged fasting.There is now substantial evidence that the term KH describes a variety of conditions including both the lower end of the normal distribution of fasting tolerance in young children as well as numerous rare disorders that impair fasting adaptation. Recent advances in molecular genetic testing have led to the discovery of these rare disorders. Idiopathic pathological KH is a diagnosis of exclusion that describes rare children who have abnormally limited fasting tolerance, experience recurrent episodes of KH, or develop symptoms of hypoglycemia despite elevated ketone levels, and in whom an explanation cannot be found despite extensive investigation. This review provides an approach to distinguishing between physiological KH and pathological KH and includes recommendations for management.

Introduction

Beyond the newborn period, hypoglycemia in a healthy child is rare, and incidental discovery of hypoglycemia in an emergency department (ED) during an intercurrent illness is uncommon [1–4]. Ketotic hypoglycemia (KH) is

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the most common cause of hypoglycemia presenting to an ED in a previously healthy child between 6 months and 6 years of age and is typically the result of decreased oral intake due to an intercurrent illness, especially a gastrointestinal illness with vomiting and prolonged fasting [2–5].

While it is common for sick children to have a decreased appetite and experience vomiting and diarrhea, hypoglycemia (defined as a plasma glucose concentration ≤50 mg/dL) is distinctly uncommon. An accurate estimate of the frequency of incidental hypoglycemia is difficult to ascertain because prospectively obtained data are virtually nonexistent and retrospective studies have used various definitions of hypoglycemia. A prospective study of 52,189 children presenting to an urban Children's Hospital ED found that among the 8,928 children in whom plasma glucose was measured, 40 (0.45%) or 1:1,304 children attending the ED had previously unrecognized hypoglycemia (plasma glucose <50 mg/dL) [1]. Of those study participants who had a comprehensive endocrinologic and metabolic evaluation, 23/32 (72%) had no identifiable pathology and were considered to have physiological KH. Subsequently, a retrospective examination of the incidence of nondiabetic hypoglycemia (identified by ICD-9 billing codes, plasma glucose concentrations were not defined) among 276,313 patients presenting to another large urban Children's Hospital ED over a period of more than 5 years was 0.034% (95% confidence interval 0.027–0.041%) [2]. A more recent study at a large urban Children's Hospital in the USA that served 224,125 children during a 2-year period found 160 cases (0.82%) of previously undiagnosed hypoglycemia among 19,506 children who had their blood glucose concentrations measured in the hospital laboratory, i.e., 1:1,400 (0.07%) of all children seen in the ED [3]. Similarly, a retrospective study conducted at a tertiary care pediatric hospital in Rome, Italy found the prevalence of hypoglycemia (venous plasma glucose <45 mg/dL) among 405,117 children and adolescents admitted to the pediatric ED to be 402 children or 0.99 per 1,000 children [4]. Overall, in these three large studies hypoglycemia (<45–50 mg/dL) occurred in approximately 1:1,133 patients in the ED setting indicating that it is a rare but important problem [1, 3, 4].

Adaptation to Fasting in Children

The metabolic and hormonal responses to fasting, which have been extensively studied in adults [6–8], are similar in children but occur at an accelerated, age-dependent rate [9]. This may be attributed to the 3-fold higher rate of basal glucose turnover in children below the age of 6 years as compared to adults (mean 7.1 vs. 2.3 mg/kg per min) [10]. After the postprandial absorptive phase of glucose homeostasis, as glycogen reserves are depleted and plasma glucose concentrations begin to decline, physiologic adaptation is mediated by a complex interplay of hormones that regulate fuel metabolism leading to the mobilization of fat stores (lipolysis) resulting in elevated plasma free fatty acid levels, mitochondrial fatty acid oxidation, elevated ketone concentrations, and decreased glucose utilization [8]. Glycogen depletion occurs more rapidly and accelerated lipolysis and ketogenesis occur after a shorter duration of fasting in younger than in older children ("accelerated starvation"), which is reflected in their lower plasma glucose and higher ketone concentrations after comparable durations of fasting (Tables 1, 2) [11, 12]. The response to fasting in older children and adolescents is similar to that of adults.

Nonetheless, most well-nourished, healthy infants and children can maintain normal plasma glucose levels after fasting for 15–18 h [11, 12], but their plasma glucose concentrations gradually decrease when the duration of fasting is prolonged beyond 15–30 h [9, 11–16]. In a recent study of 94 healthy children undergoing an overnight fast before elective surgery (mean age 8.3 ± 5.7 years (SD), range 6 months–18.7 years), mean plasma glucose was 90 ± 9.5 mg/dL (SD) and serum beta-hydroxybutyrate (BOHB) 0.25 ± 0.23 mmol/L (SD) [17]. The 19 children ≤3 years of age had significantly higher mean serum BOHB levels compared to the 75 children >3 years, 0.40 ± 0.06 mmol/L versus 0.21 ± 0.02 mmol/L, respectively. Fasting serum BOHB >1.0 mmol/L (maximum value 1.2 mmol/L) occurred in only 2 children who fasted for 13.2 and 14.1 h. These observations suggest that a serum BOHB value >1.0 mmol/L after an overnight fast should raise suspicion for pathological ketosis [17].

It is important to appreciate that ketosis and hypoglycemia are not always synonymous with pathological KH but are nonspecific biochemical features of hypoinsulinemia, which leads to mobilization of free fatty acids and hepatic ketogenesis. The constellation of hypoglycemia and ketosis is observed in numerous disorders (Table 3). Therefore, when a child presents to an ED with hypoglycemia and ketosis after a variable period of food deprivation, as often occurs during an intercurrent illness, it may be challenging to distinguish between normal physiologic KH ("accelerated starvation") and the pathological causes of KH listed in Table 3.

Table 1. Reference values of blood glucose and BOHB values during fasting

	Age								
	1–12 months (n = 12)			1–7 years (n = 27)			7–15 years (n = 9)		
Fasting duration, h	15	20	24	15	20	24	15	20	24
Glucose, mg/dL	85 (70–95)	70 (63–83)	65 (49–81)	79 (63–86)	63 (50–77)	59 (50–68)	85 (79–88)	77 (68–88)	68 (54–77)
BOHB, mmol/L	0.4 (0.1–1.0)	1.1 (0.5–2.3)	1.8 (1.1–2.8)	0.6 (<0.1–0.9)	1.8 (0.8–2.6)	2.5 (1.7–3.2)	0.1 (<0.1–0.3)	0.4 (<0.1–0.8)	0.9 (0.5–1.3)

Results are mean (10th–90th percentiles); adapted from Bonnefont et al. [11]. BOHB, β-hydroxybutyrate.

Table 2. Metabolic parameters at different ages after fasting for 20-h

Age, months (n)	0–24 (18)	25–84 (60)	85–216 (36)
Glucose, mg/dL	59 (50–70)	72 (54–86)	76 (59–94)
Acetoacetate, mmol/L	0.42 (0.38–1.05)	0.46 (0.13–0.91)	0.29 (0.09–0.81)
3-hydroxybutyrate, mmol/L	2.23 (0.91–3.31)	1.19 (0.36–2.56)	0.62 (0.09–2.18)
FFA, mmol/L	2.15 (1.03–3.24)	1.56 (0.91–2.34)	1.48 (0.70–2.66)

n, number of subjects; median (10th–90th percentile); adapted from [12].

What Is Idiopathic KH?

In 1924 Ross and Josephs, in their article "Observations on the metabolism of recurrent vomiting," published the first description of the condition now commonly referred to as KH [34]. Four decades later, in 1964, Colle and Ulstrom described 8 children "with sporadic attacks of symptomatic hypoglycemia in whom the attacks can be provoked by a short period of carbohydrate deprivation." They observed a constant association of ketosis preceding the onset of symptoms and low blood sugar values. Long intervals of normal blood sugar levels and good health intervened between the short periods of metabolic derangement. The clinical disease could be reproduced by feeding the children a low-calorie ketogenic diet; affected children developed ketosis and hypoglycemia and experienced symptoms of hypoglycemia, including seizures, in the early morning. They referred to the condition as KH [35]. However, as described above, it is now well understood that ketosis and hypoglycemia are normal physiologic responses of young children to prolonged fasting. It is notable, however, that in their initial description of KH, some children had symptoms and signs of neuroglycopenia, suggesting a subset in whom hypoglycemia and ketosis may be a pathologic disorder and not simply starvation-induced ketosis [35].

Whereas KH is the most common type of childhood hypoglycemia after the first year of life, it remains incompletely understood [13, 36–44]. The condition usually presents in the second or third year of life (onset as early as 6 months has been reported) as recurrent episodes of morning hypoglycemia. Mild forms of the disorder usually remit by the age of 8 or 9 years. The classic history is that of a child, more often a boy with a history of low birth weight, who has not eaten well the previous day or missed an evening meal, or has been unusually physically active, is difficult to rouse from sleep the next morning, and displays neuroglycopenic symptoms ranging from lethargy to seizures. In contrast to hypoketotic hypoglycemia caused by dysregulated insulin secretion, physiologic KH is not observed in the postabsorptive state but typically occurs only after a period of carbohydrate deprivation. Episodes of hypoglycemia are especially likely to occur during an illness when food intake is decreased or when vomiting and diarrhea impair the absorption of nutrients. However, a small proportion of children do not have a history of prolonged fasting beyond that which is typical for age (refer to Tables 1, 2) and in whom a physical examination and biochemical testing do not identify any of the rare causes of hypoglycemia listed in

Table 3. Causes of KH in children

Physiological
Prolonged fasting associated with acute illness (e.g., gastroenteritis)
Pathological
IPKH
Hormone deficiencies
Growth hormone deficiency
Growth hormone resistance (Laron syndrome)
IGF1 deficiency
ACTH deficiency or resistance
Adrenal insufficiency
Metabolic [18]
Glycogen storage diseases (GSD)
Glycogen synthase deficiency (GSD 0a)
Glycogen debranching enzyme deficiency (GSD III)
Glycogen phosphorylase deficiency (GSD VI)
Phosphorylase kinase deficiency (GSD IX)
Disorders of gluconeogenesis
Fructose-1,6-bisphosphatase deficiency
Pyruvate carboxylase deficiency
Phosphoenolpyruvate carboxykinase deficiency
Phosphoglucomutase I deficiency [19]
Disorders of amino acid metabolism (organic acidemias)
Maple syrup urine disease
Propionic acidemia
Methylmalonic acidemia
Disorders of the carnitine shuttle and mitochondrial fatty acid oxidation [20]
Disorders of ketone transport and metabolism [21]
Monocarboxylate transporter 1 (MCT 1) deficiency
Succinyl CoA oxoacid transferase deficiency
Mitochondrial acetoacetyl-CoA thiolase (beta-ketothiolase) deficiency
Miscellaneous metabolic causes
Carbonic anhydrase VA [22]
TANGO 2 defect (with hyperammonemia) [23]
Respiratory chain defects [24]
Syndromic/genetic conditions that may be associated with idiopathic KH or growth hormone or cortisol deficiency
Silver-Russell syndrome [25]
Prader-Willi syndrome [26]
Fanconi-Bickel syndrome [27]
Down syndrome [28]
Cenani-Lenz syndrome [29]
CHARGE syndrome
DAVID syndrome (deficit in anterior pituitary function with variable immune deficiency) [30]
Chronic diseases
Malnutrition
Malaria [31]
Medications
Propranolol [32]
Miscellaneous causes of pathological KH* [33]
Gene variants in:
Nuclear receptor corepressor 1 (*NCOR1*)
Insulin-like growth factor 2 binding protein 1 (*IGF2BP1*)
Solute carrier family 5 member 2 (*SLC5A2*) the gene encoding sodium-glucose cotransporter 2, SGLT2
Mitosis gene A-related kinase 11 (*NEK 11*)

Citations are provided to recently recognized rare causes of KH. *Suggested but not well-established causes of KH [33].

Table 3. Moreover, as Haymond and Pagliara pointed out, these children develop symptoms of hypoglycemia despite high ketone levels, whereas normal children have the same biochemical findings but without the symptoms of hypoglycemia [42]. It is these children who need further evaluation to better understand their differences in fasting adaptation that result in hyperketonemia with or without significant hypoglycemia [45] and symptoms.

Pathophysiology

Colle and Ulstrom [35] proposed that the cause of KH was impaired adaptation to fat metabolism when the supply of carbohydrates is diminished. Senior and Loridan [36] found no significant differences in the response to a ketogenic diet, followed by a prolonged fast in children who had a history of KH compared with control children, and showed that gluconeogenesis from glycerol was unimpaired. The major finding was that children with KH, compared with control children, were unable to sustain normal blood sugar concentrations during a prolonged fast [36, 39]. Pagliara et al. [38] showed that on a normal diet, overnight fasting plasma glucose was significantly lower (68 ± 4 vs. 81 ± 3 mg/dL) and blood BOHB significantly higher (1.22 ± 0.37 vs. 0.18 ± 0.08 mmol/L) in KH children than in controls. After being fed a provocative hypocaloric low carbohydrate diet, within 8–16 h children with KH developed symptomatic hypoglycemia (33 ± 3 mg/dL) and ketosis (BOHB 3.70 ± 0.32 mmol/L). In contrast, plasma glucose levels in normal children 15 h after beginning the provocative diet were 60 ± 5 mg/dL, and even after 32–36 h on the hypocaloric low carbohydrate diet maintained higher plasma glucose (48 ± 2 mg/dL) and lower BOHB (2.56 ± 0.44 mmol/L) concentrations. After initiation of the provocative diet and at the time of hypoglycemia (after 8–16 h), children with KH showed no glycemic response to glucagon, indicating depletion of hepatic glycogen stores [38]. The inability of children with KH to maintain normal blood glucose levels when fasting or while consuming a carbohydrate-deficient diet for approximately 24 h suggested a functional defect in hepatic gluconeogenesis. Subsequently, Haymond et al. [46] showed that it is the hypocaloric nature of the ketogenic diet and not its high-fat content that induces hypoglycemia in children with idiopathic KH. Chaussain et al. [13] confirmed that children with a documented history of KH (with a seizure) differed from comparably aged healthy control children in their inability to sustain normal blood glucose concentrations during a 24-h fast. Their glycemic response to glucagon was similar in the fed state but was significantly attenuated after fasting, suggesting more rapid depletion of hepatic glycogen and, similarly, suggested that the inability to sustain blood glucose concentrations could be attributed to deficient gluconeogenesis. The observed differences in fasting tolerance between younger and older children (and adults) are attributed to relatively greater energy utilization in younger children. This may be due to the greater mass of the brain relative to body size and the high glucose utilization rate in young children as compared to adults [10], which leads to more rapid depletion of glycogen during fasting and earlier onset of adaptation to fat mobilization and ketogenesis [39].

Although it has been nearly 60 years since the publication by Colle and Ulstrom [35], there has been only modest progress in our understanding of the pathophysiology of KH. Is KH caused by a specific disorder of fasting adaptation or is it simply the lower end of the normal distribution of fasting tolerance in young children as Boris Senior suggested 50 years ago [39]? Studies of glucose kinetics using a stable radioisotope have shown that KH is caused by failure to sustain endogenous hepatic glucose production and is not caused by increased rates of glucose utilization in the fasting state [43, 44]. Glucagon induces a normal glycemic response in affected children during the fed state but not at the time of hypoglycemia, indicating that the glycogenolytic pathway is intact. Infusions of alanine, fructose, or glycerol raise the plasma glucose concentration without significant changes in blood lactate or pyruvate levels, indicating that the entire gluconeogenic pathway from the level of pyruvate is intact, and suggesting that the inability to sustain normal plasma glucose concentrations may be caused by a deficiency of substrate rather than a defect in gluconeogenesis [38, 46]. Children with KH have reduced plasma alanine concentrations after an overnight fast, which decrease further with prolonged fasting [41, 46].

Alanine is the major amino acid used for gluconeogenesis. Its formation and release from muscle during periods of caloric restriction are enhanced by the presence of a glucose-alanine cycle, as well as by de novo formation from other substrates such as branched-chain amino acids. Hypoalaninemia in KH probably reflects accelerated starvation and increased utilization as a gluconeogenic precursor, rather than a specific defect in alanine metabolism. As was highlighted in the original description of KH, the children are frequently but not always smaller than age-matched controls [35]. Thus,

KH may be the consequence of a relatively small muscle mass at an age when glucose demands per unit of body weight to support brain metabolism are relatively high; i.e., children with KH may represent the lower end of the normal range for fasting tolerance [39]. Spontaneous remission of KH by age 8–9 years in most cases of physiological KH might then be explained by the increase in muscle bulk relative to brain size, with a resultant increase in the supply of endogenous substrate as well as the relative decrease in glucose requirement per unit of body mass with increasing age [10]. The plasma levels of hormones that stimulate gluconeogenesis and counter hypoglycemia (glucagon, cortisol, and growth hormone) are appropriately elevated and insulin levels are appropriately low [36, 37, 46, 47].

There is now substantial evidence that the term KH describes a variety of conditions, including both the lower end of the normal distribution of fasting tolerance in young children as well as numerous rare disorders that impair fasting adaptation (Table 3). Many of these rare disorders have been discovered by advances in molecular genetic testing such as whole exome sequencing or gene panels that include more than 120 genes involved in glucose regulation. These include, e.g., rare forms of glycogen storage diseases in patients without obvious liver enlargement who had recurrent episodes of KH [48], and patients with variants in monocarboxylate transporter 1 (MCT1), the protein responsible for transporting ketones across the blood-brain barrier [49] (Table 3). It can be hypothesized that a combination of monoallelic variants in multiple steps of glucose homeostasis, a concept referred to as synergistic heterozygosity, accounts for a subset of individuals with idiopathic KH [50].

We recommend that the term idiopathic pathological KH (IPKH) be used to indicate a diagnosis of exclusion that describes rare children who have an abnormally limited fasting tolerance (defined as BOHB >1 mmol/L within 12 h of fasting) [17], experience recurrent episodes of KH or develop symptoms of hypoglycemia despite elevated ketone levels >2 mmol/L, and in whom an explanation cannot be found despite extensive investigation. A thorough evaluation of children with presumed KH (described below) with careful exclusion of alternative diagnoses should be the initial step in their management.

Evaluation

Whether hypoglycemia discovered incidentally during an intercurrent illness in children requires an endocrinologic and metabolic evaluation continues to be controversial. Based on observations from a retrospective study of the medical records of children with hypoglycemia (identified using ICD-9 billing codes) seen in an ED of an urban children's hospital in the USA, Pershad et al. [5] concluded that in "a typical case of idiopathic KH (previously healthy, 1–5 years old, normal growth and development, no hepatomegaly, resolution of symptoms with administration of glucose) who presents with an episode of symptomatic fasting hypoglycemia an extensive and overzealous workup for an endocrinopathy or inborn error of metabolism is not necessary." In a retrospective analysis of 62 children referred to a pediatric endocrinologist for evaluation of KH, 4 of 62 (6.5%) were found to have a specific diagnosis of an endocrinologic or metabolic disorder [51]. Kaplowitz and Sekizkardes [51] recommended that in the typical setting of a previously healthy 0.5–6-year-old child with an uncomplicated episode of KH following poor food intake caused by an intercurrent illness and a normal examination (including growth), hormonal and metabolic testing can be deferred; frequent recurrences and atypical features, however, should prompt further investigation. This recommendation is at variance with that of White et al. [3] who recommended that all children with hypoglycemia of unknown etiology presenting to an ED should have a critical blood sample drawn (Box 1) at the time of hypoglycemia (blood glucose <50 mg/dL) or be admitted for a diagnostic evaluation. This conclusion was based on the observation that 10% of patients with previously undiagnosed hypoglycemia presenting to an ED had a serious, life-threatening form of hypoglycemia.

In a recent single-center retrospective study performed at a major referral center for hypoglycemia disorders, Rosenfeld et al. [52] conducted a review of 145 children referred (during an 8-year period from January 2013 to December 2018) for evaluation of hypoglycemia (defined as plasma glucose <70 mg/dL) in the setting of an acute illness. A hypoglycemia disorder was identified in 12 patients (8% of the cohort, 17% of those who underwent a diagnostic fast) and, notably, a specific diagnosis was only established after performing a diagnostic fast. The authors recommended that "all children with hypoglycemia in the setting of an illness undergo a guided diagnostic evaluation" [52]. These differences in recommendations can be reconciled by the fact that both the White et al. [3] and Rosenfeld et al. [52] studies evaluated all children with hypoglycemia, whereas Kaplowitz and Sekizkardes [51] only included children with KH in their retrospective study. In those studies that included all children with hypoglycemia,

Box 1. Critical sample at time of hypoglycemia

Plasma

- Glucose
- Insulin
- Cortisol
- Growth hormone*
- Free fatty acids
- BOHB
- Lactate
- Ammonia
- Acylcarnitine profile

Urine

- Organic acids
- Toxicology screen only if there is a clinical suspicion

*If growth is abnormal.

most patients with a serious underlying etiology for their hypoglycemia had hypoketotic hypoglycemia.

Thornton and Hawkes recently suggested that a cost-effective, compromise approach consisting of screening plasma glucose and BOHB concentrations rather than a full critical sample (see text box) on all children who present to an ED with hypoglycemia would allow differentiation of children with hypoketotic hypoglycemia, which is always pathological, from those with KH [53]. Based on the context and duration of fasting, growth parameters, and the physical examination, the physician should determine if there is any evidence of a pathological form of KH (Table 3). The physical examination is important to look for evidence of hormonal deficiencies such as short stature (growth hormone deficiency), hyperpigmentation (primary cortisol deficiency), and an enlarged liver (glycogen storage diseases). Prolonged fasting due to intercurrent illness is an important clue to the presence of physiological ketosis; whereas ketosis with short fasting duration is concerning for a pathological cause of KH. For those children who appear to be normal but have a second episode of KH, an investigation seeking the rare metabolic conditions that cannot be diagnosed with a critical sample must be undertaken (Fig. 1).

It is important to note that several of the pathologic causes of KH (i.e., ketotic forms of glycogen storage disease, MCT 1 deficiency, and ketone utilization defects) may have a normal physical examination and may not always be diagnosed on a critical sample obtained at the time of a spontaneous episode of hypoglycemia. Consequently, there still is a role for a controlled fasting study when pathologic KH is suspected, and although a fasting study may not reveal a specific diagnosis it will show premature development of ketosis (a hallmark of pathological KH). A serum BOHB concentration exceeding 1.0 mmol/L overnight should be considered suspicious for the ketotic forms of GSD and other pathologic causes of KH [17].

Assessment of children with recurrent KH may also include dynamic methods. Continuous glucose monitoring cannot be used to diagnose hypoglycemia but may provide useful information showing patterns of glycemia in conjunction with capillary BOHB concentrations measured with a portable ketone meter [54]. In cases of recurrent KH with a normal (non-diagnostic) critical sample, a controlled fasting study (see below) will demonstrate rapid development of ketosis and hypoglycemia compared to normal, age-matched children who can fast for 18–24 h without developing hypoglycemia (Tables 1, 2). When pathology is suspected based on evidence obtained from a combination of the critical sample, dynamic monitoring, and a fasting study, molecular genetic studies are recommended to confirm the diagnosis and elucidate the specific etiology. Before a controlled fasting challenge is performed, however, other possible etiologies especially disorders of fatty acid oxidation must be excluded due to the risk of sudden (cardiac) death or liver dysfunction, particularly with medium- and long-chain disorders of fatty acid oxidation. Therefore, baseline metabolic studies including plasma acylcarnitine profile and urine organic acids must be obtained before performing a controlled fasting study. Fasting tests using a standard protocol [55–57] should only be performed in a controlled setting under the careful observation of trained staff. It is imperative carefully to monitor glucose concentrations throughout the fast. Whereas some fasting protocols only obtain a critical sample when hypoglycemia occurs, assessing blood BOHB concentrations throughout the study provides valuable information regarding when glycogen stores are depleted and enhanced fat mobilization and ketogenesis commences. We recommend the placement of an indwelling intravenous line to ensure that the critical blood sample can be obtained in the setting of a stress response and that glucose can be rapidly administered if necessary. Provided that growth is normal, growth hormone levels obtained as part of the evaluation of KH during a controlled fasting test are not likely to be helpful because values ≤7.5 ng/mL are common at the time hypoglycemia [58, 59]. Likewise, serum cortisol values obtained during spontaneous hypoglycemia may not be elevated to ≥18 μg/dL. In one study, peak serum cortisol was <18 μg/dL in 61% of 76 children who had a fasting study [59].

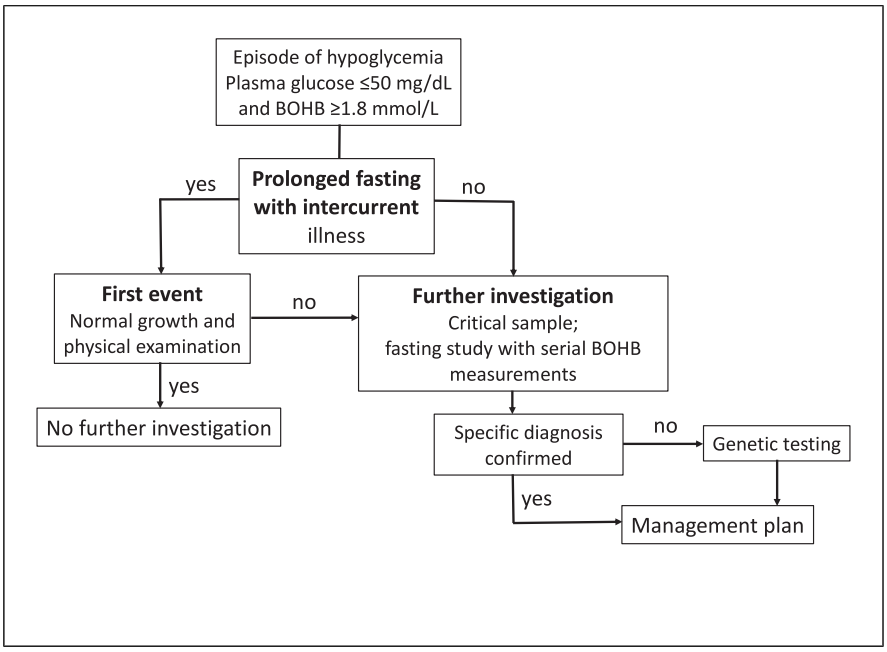

Fig. 1. Approach to the management of a child presenting to an ED with KH. At many European centers, hypoglycemia is defined as ≤3 mmol/L (54 mg/dL). See text for details. Tables 1 and 2 show expected durations of fasting tolerance in different age groups. Prolonged fasting may be defined as >15 h, >24 h, and >24–36 h in children aged <1, 1–5, and >5 years, respectively. Further investigation should include monitoring fasting plasma glucose and BOHB concentrations. Overnight fasting plasma BOHB ≥1 mmol/L may indicate a pathologic cause of KH and should prompt a more comprehensive evaluation. If necessary, a diagnostic fasting study should be performed when the child is healthy and eating normally to define the evolution of ketosis (and safety parameters for management) and to obtain a critical sample in a controlled setting if this was not already obtained at the time of spontaneous hypoglycemia in the ED.

Differential Diagnosis

IPKH should be considered a diagnosis of exclusion because, as previously noted, episodic hypoglycemia with ketosis can occur with hormone deficiencies and a variety of inherited metabolic disorders and syndromes (Fig. 2; Table 3). Recurrent episodes of KH that cannot be explained by intercurrent illness and interruption of the child's usual pattern of feeding should prompt reevaluation for a possible underlying disorder that might have been previously missed. Among the disorders that deserve special consideration are the "milder" glycogen storage diseases without obvious hepatomegaly (e.g., type IXa GSD due to X-linked phosphorylase kinase deficiency, *PHKA2*) [45, 48], adrenal insufficiency (e.g., due to inhaled or intranasal glucocorticoids), or defects in ketone utilization such as deficiency of MCT1 encoded by *SLC16A1* [49].

Distinguishing between relatively common benign physiologic ketosis with hypoglycemia and uncommon or rare pathological causes of KH is a critical part of the diagnostic evaluation of disorders of carbohydrate metabolism. The term pathological KH indicates a disorder that impairs normal fasting tolerance for the child's age (Tables 1, 2). Recurrent hypoglycemia, seizures in the setting of ketosis, or severe neuroglycopenic symptoms (e.g., lethargy) despite typical dietary intervention (a bedtime snack and overnight fasting for not longer than 10–12 h) should raise suspicion that the child has pathologic KH that warrants more intensive management. The small number of children in whom no cause can be found despite extensive biochemical and molecular genetic investigations and a clinical presentation not consistent with benign physiologic ketosis with hypoglycemia are labeled as having IPKH.

Management

In addition to their diagnostic utility, the controlled fast provides valuable information about the minimal fasting duration that is safe for an individual child, timing of the onset of ketosis, and the rate at which plasma glucose concentrations decrease before the fast is terminated. Management of physiological KH primarily consists of dietary counseling. Children with physiological KH typically are only vulnerable during episodes of acute illness (or prolonged fasting for any reason) and do not require daily glucose or ketone monitoring. Hypoglycemia can usually be prevented by avoiding prolonged fasting. In contrast, children with pathological KH may need to monitor both glucose and ketones unless the cause of pathological KH is treated, e.g., GH replacement for GH deficiency and oral hydrocortisone for adrenal insufficiency. The duration of the overnight fast should be shortened to less than 10–12 h with the routine addition of a bedtime snack containing carbohydrates and protein, and the child should eat breakfast soon after awakening in the morning. The goal

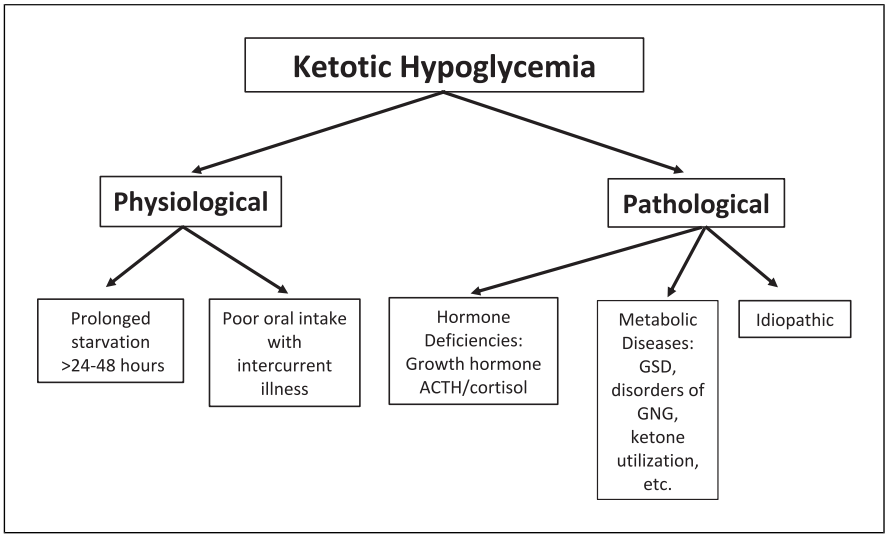

Fig. 2. GSD, glycogen storage disease; GNG, gluconeogenesis (adapted from Thornton and Hawkes [53]).

of treatment is to consistently maintain overnight fasting plasma glucose >70 mg/dL and BOHB <0.4 mmol/L. When there is an intercurrent illness, parents should measure blood glucose concentrations and test the child's urine for ketones or, preferably, measure serum BOHB concentrations using a specific blood ketone meter. The appearance of hyperketonemia precedes the onset of hypoglycemia by several hours and alerts parents to the urgent need for oral carbohydrates.

Children with IPKH may benefit from daily biochemical monitoring with an accurate point-of-care glucose meter and a blood ketone meter aiming for overnight fasting serum BOHB levels <0.4 mmol/L. These children may also benefit from a high protein diet (2–3 g/kg/day), which provides additional substrate for gluconeogenesis and prevents muscle catabolism, combined with supplemental slowly digested carbohydrates such as uncooked cornstarch or, for children >5 years of age, Glycosade® (off label use in children >2 years old has been reported). Muscle cramps in children with KH suggest the need for additional protein supplementation [60].

Nausea and vomiting caused by ketosis may lead to a vicious cycle of decreasing blood glucose concentrations and increasing hyperketosis, which can only be arrested by the administration of glucose. If oral carbohydrates (including buccal dextrose gel) cannot be tolerated, the child should be taken to an ED for intravenous glucose to raise plasma glucose to ≥70 mg/dL. Intravenous 10% dextrose at ×1.25–1.5 the usual maintenance rate for the child's weight will invariably raise plasma glucose and insulin concentrations and arrest lipolysis and ketogenesis.

Even if a specific diagnosis cannot be made each patient should have an individualized treatment plan both for routine days and sick days, and parents should be provided with an emergency letter to guide management when their child requires emergency medical care. The emergency letter provided by the child's specialist should explain the child's condition and include specific treatment recommendations that will expedite the ED response. See www.emergencyprotocol.net, e.g., that can be modified according to the unique characteristics of a specific child.

Although there are no randomized controlled clinical trials of continuous glucose monitoring in children with KH disorders, nonetheless, anecdotal experience suggests they may have some utility by alerting parents to rapidly decreasing glucose values and impending hypoglycemia, which must always be confirmed by a finger-stick blood glucose measurement. In rare, unusually severe cases where overnight fasting causes KH, one may consider a gastrostomy tube for bolus or continuous overnight feeding [61].

Conclusions

Hypoglycemia occurs in approximately 1:1,000–1:1,400 children attending EDs [3, 4] and most have physiological KH. A small percentage, however, has underlying conditions that cause pathological KH. A comprehensive diagnostic evaluation should be undertaken in children with KH who have a history of a short duration of fasting, abnormal findings on physical examination, abnormally limited fasting tolerance (defined

as BOHB >1 mmol/L within 12 h of fasting), a history of neuroglycopenic symptoms despite hyperketonemia (>2 mmol/L), or recurrent episodes of KH despite a dietary plan to prevent these episodes. Although uncommon, IPKH is not a benign condition and must be regarded as a distinct entity requiring intensive therapeutic intervention to prevent recurrent hospitalizations. Parents should have a written emergency protocol provided by the child's specialist for use at home and to expedite ED management.

Conflict of Interest Statement

J.W. is compensated for services as a member of the Central Independent Committee for the DTX401-CL301 study sponsored by Ultragenyx Pharmaceuticals and receives royalties for service as a section editor for UpToDate. D.D. is an employee of Evidera (PPD), a contract research organization. No funding from Evidera, PPD, or related entities was received for this publication. T.G.J.D. for all private-public relationships, all contracts are via UMCG Contract Research Desk, and all payments are to UMCG. There are confidentiality agreements with third parties. In the past 36 months, there have been consultation agreements (with Danone, Ultragenyx Pharmaceutical Inc, ModernaTX Inc, and Beam Therapeutics), contracts for financial research support for investigator-initiated research (NCT04311307) and sponsor-initiated research (NCT03517085, NCT03970278, NCT05139316, and NCT05196165), honoraria for lectures or presentations (by MEDTalks, Prelum, and Danone), and participation in a Data Safety Monitoring Board (NCT05095727) and Advisory Boards (Ultragenyx Pharmaceutical Inc, ModernaTX Inc, and Beam Therapeutics). P.S. has received honoraria for lectures/advisory from Novo Nordisk and Merck. He also serves as Patron of Children's Hyperinsulinism Charity (CHC) UK. P.S.T. has received research funding from Zealand Pharmaceuticals, Rezolute, Spruce and consulting fees from Zealand, Rezolute, Spruce, Neurocrine, Crinetics. D.A.W. has consulted for the following companies over the past 3 years: Ultragenyx, Beam Therapeutics, Prime Medicine, Moderna, Danone, Alltrna, Golden Heart Flower, Exsilio Therapeutics, Grace Science, Zip Bio, Chaim Medicine, Vitaflo, Siren Biotechnology, and Cometa Therapeutics. He also served as SVP at Passage Bio and interim GMO at Grace Science during this period.

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Author Contributions

J.W. reviewed the literature, created a first draft, and was responsible for the final submitted version of the manuscript. T.D., D.D., P.S., P.T., and D.W. all critically reviewed and revised the manuscript, added citations, and approved the final version.

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