Review article

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Idiopathic ketotic hypoglycemia in children: an update

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Idiopathic ketotic hypoglycemia (IKH) is defined as bouts of hypoglycemia with increased blood or urine ketones in certain children after prolonged fasting or during illness. IKH is divided into physiological IKH, which is most frequently observed in normal children with intercurrent acute illness, and pathological IKH, which occurs in children who lack counter-regulatory hormones, have a metabolic disease, or have Silver-Russell syndrome. The typical patient is a young child between the ages of 10 months and 6 years. Episodes nearly always occur in the morning after overnight fasting. Symptoms include those of neuroglycopenia, ketosis, or both. IKH may be diagnosed after ruling out various metabolic and hormonal conditions associated with ketotic hypoglycemia. Sufficient amounts of carbohydrates and protein, avoidance of prolonged fasting, and increased frequency of food ingestion are the main modes of treating IKH. It is crucial to understand the pathogenesis of IKH and to distinguish physiological IKH from pathological IKH. In this mini-review, we present a brief summary of IKH in terms of its definition, types, clinical presentation, diagnosis, and therapeutic approach in children.

Keywords: Idiopathic ketotic hypoglycemia, Ketonuria, Ketonemia, Prolonged fasting

Highlights

- IKH is defined as episodes of hypoglycemia with increased blood or urine ketones in children following prolonged fasting or during illness . I is divided into physiological IKH, which is most frequently observed in normal children , and pathological IKH. The main lines of treatment of IKH include avoiding prolonged fasting , and increased frequency of food ingestion that provide enough amounts of carbohydrates and protein.

Introduction

Idiopathic ketotic hypoglycemia (IKH) is the most common cause of hypoglycemia in nondiabetic children.[1] IKH is defined as bouts of hypoglycemia with increased blood or urine ketones in children after prolonged fasting or during illness.[2] It was originally described in 1964, when 8 children suffering from periodic episodes of clinical hypoglycemia were studied after exclusion of metabolic and hormonal diseases. A continual association of ketosis preceding symptoms and hypoglycemia was noted. The hypoglycemia was often the result of only minor alterations of the usual pattern of food intake. Long intervals of normal blood sugar values and good health occurred between short periods of metabolic derangement. The original authors reported that the first episodes of the patients rarely occurred before the age of 18 months, and that the children were below the 50th percentile for height and weight.[3] Later reports described affected children as young as 12 months with normal growth parameters.[4] IKH appears to cover a wide clinical spectrum, ranging from mild ketotic hypoglycemia (KH)

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in infancy that presents with mild symptoms and tends to improve with age to unusually frequent severe attacks that may be long-lasting and do not enter remission before the patient is school age or may even persist into adulthood.[5]

Pathogenesis

The brain relies on a constant supply of glucose as a key energy substrate since it lacks energy storage. During IKH, the brain can also utilize ketones as respiratory substrates for oxidative metabolic processes.[6] High blood ketones, on the other hand, will be eliminated in the urine together with sodium and potassium salts. Over a period of time, the body's stores of sodium and potassium salts run low, which causes poor appetite, nausea, and eventual vomiting. This establishes a vicious cycle in which the child is unable to consume sugar-rich foods or beverages, which further encourages lipolysis and the formation of ketone bodies and exacerbating KH.[2]

Classification

1. Physiological IKH

This IKH type is most frequently observed in normal children with intercurrent acute illness causing prolonged starvation and a fever-induced increase in metabolism. Additionally, it can be common in circumstances of malnutrition or severe malaria.[2,5]

2. Pathological IKH

Pathological IKH is often underdiagnosed and undertreated owing to the widespread misunderstanding that all IKH represents normal variation. Patients with pathological IKH pose a diagnostic challenge to medical professionals. It is defined as recurrent symptomatic, or occasionally symptomatic, episodes with β-hydroxybutyrate (BOHB) ≥ 1.0 mmol/L and blood glucose < 70 mg/dL (3.9 mmol/L). In the absence of prolonged fasting, acute infections and chronic conditions are known to cause KH.[2,5] Children with pathologic IKH can have euglycemic ketosis representing progressive metabolic stress prior to the development of hypoglycemia.[5] Furthermore, pathological forms of IKH can be present in children who do not produce counter-regulatory hormones, such as cortisol or growth hormone (GH); in those with metabolic conditions such as glycogen storage disease (GSD), specifically GSD 0, III, VI, and IX, and ketone transporter defects; or in those with suggested novel disease entities revealed by exome sequencing.[7]

Pathological IKH is also common in children with Silver-Russell syndrome, of whom more than one in four have KH after a simple overnight fast and are particularly susceptible during illness or surgery.[5,8] This may be attributed to the combination of their large brains compared to their bodies, poor muscle and liver mass, and feeding difficulties.[8]

Epidemiology

Data on the incidence and prevalence of IKH are sparse; however, IKH is the most common diagnosis assigned to episodes of hypoglycemia in children in emergency departments in the United States.[9] According to literature reviews, IKH has been observed to be more prevalent in boys,[2,10] who are more likely to carry mutations in the *PHKA2* gene known to be connected with IKH.[11] Furthermore, it was claimed that IKH is common in African children with chronic malnutrition or severe malaria.[12,13] Drachmann et al.[14] found for the first time a high frequency of KH in 10 (7.2%) of 139 Down syndrome (DS) patients, with a median age of 8.0 years. This finding warranted verification in different study contexts. The authors suggested screening for KH in DS patients because it is possible to prevent KH attacks, enhance growth, and avoid overeating and obesity with simple therapies such as frequent meals, increased protein intake, and cornstarch consumption.[14]

Patient criteria and precipitating factors

The age range of patients with physiological IKH is 10 months to 6 years, at which age remission is common, likely because of the increased their muscle mass and decreased glucose requirement per unit of body mass.[15] Most children affected by IKH have a thin build and a weight percentile below their height percentile without other evidence of malnutrition.[2] Such children frequently exhibit poor eating habits and have little to no tolerance for fasting.[6] IKH can be brought on by stress, viral infections, acute gastroenteritis, prolonged fasting (such as skipping supper the night before), and low carbohydrate intake the day before (such as a hot dog without a bun).[5] The majority of these children experience recognizable recurring episodes over the subsequent few years.[1] Kaplowitz and Sekizkardes[15] reviewed the charts of 150 children with hypoglycemia: 62 had a clinical diagnosis of KH (32 males and 30 females; mean age, 2.9 years). Most had a history of gastrointestinal illness or prolonged fasting, while 29% had no apparent precipitating event. Low serum CO_2 was observed in over half of the patients; however, no routine hormone testing, metabolic testing, or supervised fasting resulted in a relevant diagnosis. Four of 62 (6.5%) had relevant diagnoses that explained KH, including one child with failure to thrive, who was found to have GH deficiency, and three who were identified by genetic testing, including 1 case of GSD type 9α. Nonetheless, all had atypical presentations.

Clinical manifestations

Children with KH may exhibit a wide range of symptoms and signs, including hypoglycemia, ketosis, or both.[5,15] The neuroglycopenic symptoms usually include sweating, hunger, lethargy, malaise, sluggishness, tiredness, headache, dizziness, behavioral changes, and/or confusion. In severe cases, seizures and coma may occur. All these symptoms improve after glucose administration.[16] The manifestation of ketosis includes

nausea, vomiting, abdominal discomfort, muscle cramps, headache, lethargy, a pungent smell on the breath, and acidotic breathing. Coma may occur.[2] Children with IKH are more likely to develop cataracts than children with other types of hypoglycemia.[17] Wets et al.[18] reported that 15 (9 boys and 6 girls) of the 40 patients with KH in their study developed cataracts. Although the mechanism of cataract formation in KH is unknown, osmotic swelling of the lens fibers is most likely the cause. The authors recommended that all children with KH be referred early for an ophthalmic examination so that appropriate therapy can be implemented in a timely manner.[18]

Diagnosis

Physiological IKH may be diagnosed after ruling out various metabolic and hormonal conditions that occur with KH. It is crucial to conduct the proper investigation at the time of hypoglycemia to exclude other causes.[16,19] Plasma glucose between 35 and 60 mg/dL is usually associated with ketonuria and ketonemia.[2] On the other hand, insulin concentrations are appropriately low, which excludes the occurrence of hyperinsulinemia. Other routine tests are normal.[15] A controlled fasting test performed in a hospital setting can help establish an IKH diagnosis and provide an estimation of the severity of the condition if the IKH is not investigated during a spontaneous acute episode with severe manifestations (Table 1).[20] Depending on age, an overnight fasting study can be conducted until the BOHB is > 2 mmol/L or the glucose is 50 mg/dL. A diagnostic critical sample is obtained at the end of the fasting trial with frequent glucose and BOHB monitoring, which enables the physician to determine when the BOHB rises above 1 mmol/L and provides the child's caregivers with knowledge of the child's fasting tolerance.[15]

Table 1. Critical sample tests for ketotic hypoglycemia

Blood sample
• Glucose
• Ketones (beta-hydroxybutyrate)
• Free fatty acids
• Cortisol
• Insulin and C-peptide
• Lactate
• Carnitine/acylcarnitine
• Ammonia
• Growth hormone
• Amino acids
• Electrolytes
• Liver function tests
First urine sample voided
• Glucose, ketones
• Reducing substances
• Amino acids
• Organic acids

Adapted from Royal Children's Hospital Clinical Practice Guidelines.

1. Genetic analysis

Mutations in *PHKA2* have been detected in several children with IKH.[11] Moreover, trio exome sequencing has revealed mutations, including *SLC16A1* (*MCT1*), *NCOR1*, *IGF2BP1*, *SGLT2*, and *NEK11*, as potential novel causes in children with otherwise unexplained KH.[5]

Monitoring

The frequency and severity of IKH are monitored by bedside glucometers with ketone sticks and continuous glucose monitoring after the diagnosis of IKH has been confirmed, particularly when the patient first awakens in the morning or when they experience symptoms.[21,22]

Consequences of IKH

Chronic ketosis consequences include poor growth, hepatic transaminase elevation, and osteoporosis.[1,2] Moreover, sustained and severe hypoglycemia can cause permanent brain damage.[23]

Treatment

The management of IKH is to prevent hypoglycemia, fatty acid oxidation, and protein deficiency by providing sufficient amounts of carbohydrates and protein. It involves avoidance of prolonged fasting, increased frequency of feedings, and close monitoring of oral intake, particularly during stressful situations or periods of high activity.[24] Giving the child a bedtime snack of carbohydrates (such as cornstarch, long-release corn starch, raw corn flour dissolved in a drink, spaghetti/pasta, or milk) will help prevent prolonged fasting. The child should also be awakened and fed after the usual duration of sleep.[1,2] Gastrostomy tubes for bolus or continuous tube feedings are relatively well-tolerated and effective treatments and are indicated in children with severe and frequent KH who are unable to maintain fasting for any significant length of time.[25] If a crisis occurs, the child should be given carbohydrates, such as glucose tablets or gel, juice, sugary candy, fruit juice, regular (not diet) soda, honey, or buccal carbohydrate gel, to raise the blood glucose level. If there is no improvement or the child is unable eat or drink owing to vomiting, tiredness, or seizures, intravenous fluids containing dextrose or intramuscular glucagon may be needed.[1,2,16]

Prognosis

IKH remission is typically believed to occur between the ages of 6 and 7 years and is rare after the age of 9 years.[2] Children who demonstrate hypoglycemia after puberty should be exposed to further investigations to determine the underlying etiology.[5,16]

Conclusions

IKH is a serious endocrine condition that manifests as episodes of hypoglycemia accompanied by increased blood or urine ketones in children after extended fasting or during illness. It is important to recognize children who have IKH, whether pathological or physiological. This can be achieved by performing a thorough medical history review, a physical examination, and laboratory tests.

Notes

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