# (Idiopathic) Ketotic hypoglycemia in children

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**Abstract**

Idiopathic Ketotic Hypoglycemia is the most common non-iatrogenic cause of hypoglycemia in children beyond infancy. It improves with age and is rare after puberty.

Early morning hypoglycemia, responding promptly to glucose, is a typical presentation.

Etiology of hypoglycemia is unclear; deficiency of gluconeogenic substrate (hypoalaninemia) has been widely proposed.

Idiopathic Ketotic Hypoglycemia is a diagnosis of exclusion. Rule out specific etiologies first.

Ketonuria precedes hypoglycemia by several hours, testing for ketonuria helps in early detection.

For prevention, avoiding fasting states and bedtime snacks are helpful.

**Keywords:** Ketotic hypoglycemia, children, hypoalaninemia

## Introduction

'G, a 4 yr old developmentally normal girl, presented with recurrent seizures (3 episodes) for the past three months. The seizures were generalised tonic clonic in nature, preceded by vomiting early in the morning and responding immediately to glucose. There was no suggestive past, neonatal or family history. Clinical examination, baseline biochemical, neurological investigations in the interictal period when the child was referred to us was normal. Fasting test resulted in blood sugar of 26 mg/dl with ketonuria at the end of 18 hours. Child responded promptly to oral glucose. There was no hyperinsulinemia.'

This is a typical case scenario of Idiopathic Ketotic Hypoglycemia (IKH), also known as Accelerated Starvation or Transient Intolerance of Fasting. It is the most common non-iatrogenic cause of hypoglycemia in children beyond infancy (1,2).

## Clinical features

Hypoglycemia is a disorder of glucose homeostasis and occurs when glucose consumption exceeds glucose production. The classic presentation is the appearance of recurrent episodes of hypoglycemia and ketosis provoked by fasting for 12 to 24 hours. Early morning hypoglycemia before breakfast especially when associated with strenuous physical activity the previous evening or during intercurrent illnesses is a classic presentation. These episodes respond promptly to glucose administration and neurological sequelae are rare.

IKH usually presents between 18 months and five years of age. It improves with age and is rarely seen after puberty. These children are usually small and thin with decreased muscle mass, born small for gestational age and may have had transient neonatal hypoglycemia (3).

## Etiopathogenesis

The etiopathogenesis of this disorder remains unclear. Glucose utilisation as well as hepatic glycogenolysis appear to be normal (4). Serum insulin levels are appropriate for the blood glucose levels (5). Inability of children with ketotic hypoglycemia to respond to glucagon after brief caloric restriction suggests involvement of the gluconeogenic system (6). The various possibilities proposed are:

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**Improper glucose production**

Deficient availability of gluconeogenic substrate: Serum alanine levels have been seen to be low at the time of hypoglycemia in children with IKH with restoration of normoglycemia and ketosis on alanine supplementation and with steroid administration (which elevated the serum alanine levels probably by protein catabolic effect) (7-9). It is unclear whether hypoalaninemia is the cause of hypoglycemia (because of a specific defect in protein catabolism or it could reflect decreased muscle mass in these thin children) or a consequence, secondary to decreased muscle glucose uptake in response to hypoglycemia and increased levels of free fatty acids and ketone bodies, which inhibit release of alanine from skeletal muscle (10). Interestingly, hypoalaninemia has not been observed in some children with IKH raising doubts as to this being the sole cause (11).

The gluconeogenic pathway appears intact; serum glucose concentration increases appropriately when alanine is infused at the time of hypoglycemia (9). The counter-regulatory hormones also appear to be intact.

After 8 to 16 hours of fasting, these children show the same metabolic pattern as normal healthy children fasted for 24 to 36 hours. Possibly, children with ketotic hypoglycemia represent the tail of the gaussian curve in the normal age-dependent development of the adaptation to starvation (12).

*Improper ketone utilisation*: It is controversial whether improper ketone utilisation has a role to play in ketosis in children with IKH as some studies have not elicited different responses with ketone administration from those seen in normal children (11,13).

**Diagnosis**

Ketosis (and ketonuria) is a normal response to fasting and a falling plasma glucose concentration, IKH should not be regarded as a specific diagnosis. This is a diagnosis of exclusion and specific etiologies of ketosis and hypoglycemia should be excluded first (Table 1). The classic clinical scenario provides the most important clue. Appearance of recurrent hypoglycaemic episodes after fasting in an otherwise normal child responding promptly to glucose should be highly suggestive of IKH. In IKH, at the time of hypoglycemia laboratory evaluation reveals ketosis, ketonuria, appropriately suppressed insulin levels and usually hypoalaninemia (Table 2).

**Management**

Hypoglycemic episodes promptly respond to glucose supplementation. Oral or intravenous

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| **Liver large** |
| Glycogen storage diseases (GSD Types I, III, VI, and IX) |
| Fanconi-Bickel syndrome (GSD XI) |
| Disorders of gluconeogenesis (e.g., fructose1,6-bisphosphatase deficiency) |
| **Liver normal size** |
| Accelerated starvation (ketotic hypoglycemia) |
| Cortisol/ACTH deficiency |
| GH deficiency |
| Panhypopituitarism |
| Glycogen synthase deficiency (GSD 0) |
| Short chain fatty acid oxidation disorders |
| Acetoacetyl CoA thiolase deficiency (84) |
| Succinyl-CoA:3-oxoacid CoA-transferase deficiencya |
| Organic acidemias (e.g., maple syrup urine diseaseand methylmalonic acidemia) |

**Table 1: Causes of Ketotic Hypoglycemia (14)**

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| Raised blood ketones |
| Ketonuria |
| Low plasma alanine concentration |
| Normal blood lactate, pyruvate levels |
| Appropriately suppressed plasma insulin levels |
| Increased counterregulatory hormones |
| Glycemic response to glucagon (0.03mg/kg IM or intravenous (IV); maximum 1 mg) is normal in the fed state, but blunted at the time of hypoglycemia |

**Table 2: Laboratory findings in Idiopathic Ketotic Hypoglycemia**

mode of glucose administration will depend on the clinical condition of the child.

**Prevention**

Family education plays a vital role. Avoidance of prolonged periods of fasting help prevent such episodes.

* Bedtime snack consisting of both carbohydrate and protein / uncooked cornstarch (1 g/kg) in milk should be given at bedtime.

* During intercurrent illness, frequent intake of carbohydrate containing drinks

* Frequent testing of blood glucose and urine for ketones during intercurrent illnesses. Appearance of ketonuria precedes the onset of hypoglycemia by several hours.

* Once ketosis is present, the child must consume adequate amounts of oral carbohydrate or intravenous glucose if necessary, to avert the development of hypoglycemia.

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