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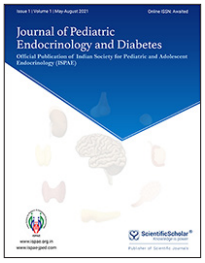

Editorial Commentary

Etiology and outcome of hypoglycemia in young children: Indian perspective

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Hypoglycemia is an important and common emergency encountered by pediatricians and pediatric endocrinologists. In the current issue of the journal, Chai *et al.* describe a study detailing causes, age distribution, and clinical presentation of 501 cases of hypoglycemia in the age group 0–6 years.[1]

Plasma glucose (PG) is maintained in a narrow range. There are only two mechanisms to prevent PG from rising, that is, insulin secretion and renal glucose excretion. On the other hand, there are several mechanisms to prevent a fall in PG. Moreover, the brain uses glucose as the main fuel for its metabolic needs and does not store glucose or glucose precursors. The brain needs a continuous supply of glucose. As the PG falls, at about 80 mg/dL, endogenous insulin secretion is shut off.[2] At a PG of about 68 mg/dL, counter-regulatory hormones are activated with enhanced secretion of glucagon and release of catecholamines. This beginning of counter-regulation is heralded by adrenergic symptoms, namely, trembling, fast pulse rate, cold skin, and cold perspiration. PG of 70 mg/dL is the alert level for evaluating hypoglycemia. As the PG continues to fall, there are symptoms due to brain dysfunction such as headache, confusion, altered behavior, convulsion, coma, and ultimately death. The neuroglycopenic symptoms usually (but not always) appear at about 54 mg/dL, and this level is used to define hypoglycemia biochemically.[2]

There is a lack of consensus regarding PG cutoff in different age groups and clinical scenarios. For example, outside the neonatal period, hypoglycemia is defined by a PG of <45 mg/dL (<2.5 mmol/L) in a well-nourished child and <54 mg/dL (<3 mmol/L) in a malnourished child.[3,4] As PG falls below 54 mg/dL for a longer duration, there is secretion of other counter-regulatory hormones, such as growth hormone and cortisol, to increase hepatic glucose output and inhibit peripheral glucose disposal so that glucose is spared for use by the brain. The body fails to keep PG above 50 mg/dL when the counter-regulation is overwhelmed.

Chai *et al.*, carried out a retrospective analysis of the laboratory database at the Royal Hospital for Children, Glasgow, over nine years (2013–2021). It led to the identification of 501 children with PG below 54 mg/dL during the study period.[1] Labeling hypoglycemia as the most common emergency in a pediatric hospital on the basis of 501 cases identified over nine years may not be justified. The authors have categorized low PG into mild (46.5–54 mg/dL), moderate (27–46.5 mg/dL), and severe (<27 mg/dL). However, the basis for the categorization of the PG cutoff into these three categories has not been explained.

There is a lack of consensus on the diagnostic cutoff of low PG in different age groups and the intervention threshold for starting treatment in patients who are symptomatic vis-a-vis those

who are asymptomatic. According to one guideline, among asymptomatic infants at risk of low PG, infants whose PG levels are <25 mg/dL (<4 h of life), <35 mg/dL (4–24 h of life), <50 mg/dL (24–48 h of life), and <60 mg/dL (>48 h of life) warrant intervention.[5,6] In the SugarFACT trial in Malawi, raising the threshold for initiating treatment of hypoglycemia from 45 mg/dL to 90 mg/dL did not alter in-hospital mortality in 322 severely sick children.[7]

Hypoglycemia represents a continuum of dynamic processes, leading to ongoing interaction between evolving low PG and the hormonal changes that try to prevent falls in PG. The development of symptoms of low PG and the development of complications and mortality are influenced by the underlying disease, duration, and severity of hypoglycemia. A single low PG value may not predict long-term outcomes.[8,9]

It is obvious that the lower the PG, the greater will be the likelihood of brain dysfunction and damage. Whipple's triad is used to identify hypoglycemia.[5,10] It comprises low PG, symptoms of low PG, and relief of symptoms of rising PG. This definition applies to older children and adolescents but not to neonates and infants who cannot verbalize their feelings or symptoms. Signs such as tachycardia, tremors, and cold skin can alert the clinical team to the possibility of the occurrence of low PG. In neonates <48 h, apnea, jitteriness, and high-pitched crying may be the features of hypoglycemia.

There are multiple etiologies attributable to persistent low PG, including increased insulin secretion, deficiency of counter-regulatory hormones, deficiency of gluconeogenic precursors, interference with gluconeogenesis, defect in the glycogenolytic pathway, severe sepsis, severe illnesses, tumor, trauma, and accelerated starvation.

History of presenting illness, family history, and clinical findings can provide clues to the likely etiopathology. Glucometers at the lower range of PG are less reliable, with as much as 20% variation between glucometer and laboratory values.[11] Hence, a low PG detected by a glucometer needs to be confirmed by parallel testing in the laboratory. A detailed evaluation is warranted in children presenting with neurological features such as altered sensorium and seizures and those presenting with prolonged or recurrent low PG. Those children with moderate to severe low PG in the present study were candidates for a full work-up.

In the present study by Chai *et al*., out of 501 patients, 28% had a full hypoglycemia screen, 38% had a partial screen, and 34% had no additional blood tests related to hypoglycemia screening.[1] The cause of hypoglycemia was identified only in 15%, with gastroenteritis being the most common cause.

A critical blood sample and first urine sample after the laboratory confirmed low PG should be collected for re-assessment. Tests for PG, insulin, C-peptide, beta-hydroxy-butyrate, lactate, ammonia, carnitine, acylcarnitine, free fatty acid, amino acid profile, cortisol, growth hormone, and electrolytes are performed in the blood sample and tests for acetone, fructose, galactose, and organic acids in the urine sample. However, all these tests may not be required in every patient.[5]

Hyperinsulinism is associated with high or inappropriately normal plasma insulin and C-peptide in the presence of low ambient PG. It is characterized by a high glucose infusion requirement to maintain euglycemia (usually >8 mg/kg/min) and the absence of lipolysis and ketogenesis (reflected by negative ketone bodies). Parenteral administration of Inj Glucagon leads to rise in PG of >30 mg/dL. Hyperinsulinism is the most common cause of hypoglycemia in the age group >48 h after birth to 2 years. Genetic workup can identify the specific congenital disability and the molecular mechanism of persistent hyperinsulinemic hypoglycemia, which will guide the appropriate intervention. The study by Chai *et al*. has not alluded to details on this aspect.[1]

Accelerated starvation (previously known as ketotic hypoglycemia) is a diagnosis of exclusion. Lack of food intake for a few days leads to low PG, ketonemia, and ketonuria. Enteral feeding rapidly corrects the symptomatology. Chai *et al*. reported that 5.2% of children were diagnosed to be affected by accelerated starvation in the present study.[1]

Hypoglycemia *per se*, particularly if severe, persistent, or recurrent, can lead to an adverse neurological outcome, or the underlying disease, which led to hypoglycemia, may lead to neurological handicaps and other disabilities. Thus, it is necessary to follow-up children for neurobehavioral assessment, disease-specific assessment, and appropriate intervention. Sometimes, the cause of hypoglycemia may not be apparent at initial evaluation, and meticulous follow-up may reveal the underlying etiology. In the present study, 48% of children with hypoglycemia had ongoing follow-up. Among those with severe hypoglycemia (PG below 27.0 mg/dL), causes were identified in 72%, and 63% of this cohort was followed up after the initial presentation.

The study provides valuable data on hypoglycemia in children. It highlights suboptimal utilization of laboratory services and inadequate follow-up of children likely to benefit from such services even at a reputed pediatric center in a developed country. There is a need to sensitize pediatricians to endocrine disorders presenting as hypoglycemia regularly.

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