Hyperinsulinemic Hypoglycemia in Neonates Due to Perinatal Stress: A Case Series

Hyperinsulinemia (HI) is a well-known cause of persistent hypoglycemia in neonates. Early diagnosis is crucial, as management needs to be aggressive because insulin blocks alternative fuels like ketones for cerebral metabolism resulting in long-term neurological sequelae. It can be persistent or transient. The persistent forms are inherited and are due to mutations in genes associated with insulin secretions regulation. The transient state; however, is non-genetic and also known as perinatal stress-induced hyperinsulinemia (PSHI). Various factors associated with perinatal stress are intrauterine growth restriction, birth asphyxia, cesarean delivery, and maternal toxemia that can lead to HI [1]. Collins and Leonard in 1984 reported cases of small for gestational age and birth asphyxia, who responded well to medical therapy, followed by spontaneous resolution [2].

We retrospectively analyzed the medical records of newborns who presented with hypoglycemia (lethargy, poor suck, or poor feeding) and biochemical evidence of hyperinsulinemia in the neonatal intensive care unit. Hyperinsulinemic hypoglycemia was defined as hypoglycemia (<50 mg/dL) with inappropriately elevated plasma insulin (>3 mIU/mL) and/or evidence of an excessive insulin effect, such as an increased glucose consumption rate (>8 mg/kg/min) and inappropriately suppressed plasma β-hydroxybutyrate (<2 mmol/L) [3]. Out of 111 babies with hypoglycemia, 14 (12.6%) babies were diagnosed to have hyperinsulinemia. All the babies were treated initially with intravenous glucose requiring a median glucose infusion rate (GIR) of 12 mg/kg/min. Diazoxide was started as soon as the diagnosis of hyperinsulinemia was made. To wean off the baby from intravenous glucose, oral diazoxide was initiated as first-line medication – 11 (78.6%) patients responded to it. Three (21.4%) babies did not respond even after maximum doses of diazoxide, following which a second-line drug, octreotide, was added. All three babies who required octreotide treatment were small for gestational age (SGA). The maximum dose of octreotide required was 14 mcg/kg/day along with diazoxide. Duration of therapy for diazoxide with octreotide ranged from 7 to 14 days. All three babies tolerated octreotide well with no adverse events.

Most of the babies were an early term with a male to female ratio of 1.3:1. Early term (71%), SGA (43%), cesarean section (71%), and fetal distress (28%) were found as risk factors for PSHI in this series. Each baby had one or more mentioned risk factors. Hoe, et al. [4] in their study of 26 neonates with prolonged HI, found it to be frequently associated with the male sex, low birth weight, perinatal stress, and cesarean deliveries; however, they could not find any risk factor in 19% of babies. Insulin levels in all our babies were elevated, with a median insulin level of 13.6 mU/L, along with hypoketonemia. However, there are reports of perinatal stress-induced hyperinsulinemia with normal insulin levels, specifically in SGA babies [4]. Response to diazoxide was consistent with previous findings [4]. In the study by Hoe, et al. [4] only 2 out of 26 babies were started on octreotide. All 3 of them were born by cesarean section and were SGA. In 2 babies, octreotide was added at a maximum diazoxide dose of 10 mcg/kg/day as they required some dextrose support to maintain their blood sugars. In one baby, octreotide was added at a maximum diazoxide dose of 15mcg/kg/day as he intermittently maintained blood sugars on feeds and diazoxide. Other authors have reported treatment time ranging from 18 to 402 days. In our study, 100% responded to medical treatment, whereas it was 80-95% in published literature [4,5]. Pan, et al. [6] reported their experience of octreotide therapy for HI in 7 cases of SGA neonates with treatment duration between 9 to 45 days, and with an excellent response to treatment in all patients. As all babies remained admitted till the treatment was completed and responded well to medications, we suspected it due to perinatal stress; therefore, genetic analysis was not considered.

To summarize, the requirement of a high glucose infusion rate in a neonate should raise suspicion for HI. Routine glucose screening of high-risk neonates can help in its early identification. Identification and appropriate treatment of a neonate with HI are essential to prevent long-term neurologic sequelae. Unlike congenital HI, neonates with perinatal stress-induced hyperinsulinism should recover with medical management within a few days to few weeks. However, larger series are required to draw firmer conclusions.

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