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Neonatal Hypoglycemia

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ABSTRACT:

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Hypoglycemia is one of the most frequent metabolic problems in neonatal period. However, controversy remains surrounding its definition and management especially in asymptomatic patients. Using different protocols, the organizations have significant differences on whom to screen and what levels of glucose should be used for treatment. A new definition is the identification of the first 48 h as a transitional hyperinsulinemic state with transient asymptomatic hypoglycemia. Today evidence does not support a specific concentration of glucose that can be diagnosed as hypoglycemia, or decided to be treated, or can result in acute or chronic irreversible brain damage.

Keywords: Asymptomatic, hypoglycemia, newborn, treatment

ÖZET:

Yenidoğan döneminde hipoglisemi

Hipoglisemi yenidoğan döneminde oldukça sık görülen metabolik sorunlardan birisi olarak kabul edilir. Bununla birlikte özellikle asemptomatik olan bebeklerde tanımlanması, ve tedavisi ile ilgili tartışmalar devam etmektedir. Kullanılan protokollerde kimlerin taranması gerektiği, hangi glikoz değerlerinin tedavi edilmesi gerektiği ile ilgili önemli derecede farklılıklar mevcuttur. Yeni bir bilgi olarak yaşamın ilk 48 saatinde geçici hiperinsülinemi ile birlikte geçici asemptomatik hipoglisemi tanımlanmaktadır. Günümüzdeki kanıta dayalı bulgular; spesifik bir kan glikoz değerini; akut veya kronik geri dönüşümsüz beyin hasarı yapmada veya hipoglisemi tanı ile tedavisini belirlemede desteklememektedir.

Anahtar kelimeler: Asemptomatik, hipoglisemi, yenidoğan, tedavi

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INTRODUCTION

It is the frequent situation encoutnered in the neonatal period, with the low blood glucose levels. However, when defining the hypoglycemia, the blood sugar should be consistently low, the measurement should be made with a device with high accuracy, and the baby shouldn't have any other reason which can be explained that causes abnormal clinical findings, beside the metabolic adjustment disorder. It is estimated to be seen in a rate of 1.3-5 /1000 live births in the neonatal period (1). Hypoglycemia is seen in about 17% of the babies that are hospitalized in the neonatal intensive care unit (NICU) (1). In the developing countries, due to higher incidence of low birth-weight and intrauterine growth restriction (IUGR), and poor nutrition and inadequate care, the incidence of hypoglycemia is estimated to be higher. The diagnosis of hypoglycemia is extremely difficult. It is not likely to diagnose it, based on only the physical examination findings of the baby. The hypoglycemia symptoms being nonspecific and subtil, and the same clinical signs which can be detected in sepsis, congenital heart diseases, prematurity, metabolic diseases and increased intracranial pressure, complicate the differential diagnosis.

Today, when all the scientific data is evaluated for hypoglycemia, the answers for:

What is the very low value?

How low is very low?

What is the limit value or duration of hypoglycemia that may cause irreversible changes in the brain functions?

When should the blood glucose level be checked after birth in babies at risk? questions are not exactly

known. There is no evidence-based practice related with how to diagnose pathological hypoglycemia and the most accurate way to monitor the blood sugar, and most of the follow-up and treatment are applied empirically.

Fetal Glucose Homeostasis

The fetus, is totally dependent on the transfer of glucose from the mother by placenta. The fetus itself does not produce glucose under normal conditions. With the glucose and the other substrates (ketone, free fatty acids and amino acids) that pass from the mother, the fetal growth and the required energy need for the metabolism are provided. It is known that independent from the gestational week, the average fetal glucose levels are 54 mg/dl, and it is about 10 mg/dl lower than the mother's blood glucose levels. The maternal insulin that regulates the maternal blood sugar, does not pass through the placenta, unlike the glucose, therefore, fetal insulin secretion determines the fetal glucose use. The primary function of fetal insülin in the intrauterine period, is the regulation of fetal growth (2).

After the birth, the blood glucose levels drop rapidly with the loss of relationship with the mother by cutting the umbilical cord; the average plasma glucose level decreases to 25-30 mg/dl in a healthy full-term baby immediately after the birth, while it increases to about 45-60 mg/dl in the first 1-2 hours of life. This situation may extend until the first 4-5 hours of life, staying at levels under 45 mg/dl (2,3). This period may be called as the "transition period". At the transition period, the maintenance of the glucose balance is dependent on many factors. These factors in order, are: the function of the glycogenolytic enzymes, the presence of adequate glycogen storage, the function of the glyconeogenic enzymes and the presence of the substrates of this pathway (ketone, free fatty acids, glycerol, lactate) and the effects of glucose regulation hormones (insulin and glucagon). In a healthy full-term baby, in the fasting situation, only the hepatic glycogen storages may provide adequate glucose support for the first 10 hours of life (4).

Transient Asymptomatic Hypoglycemia

In the studies, it was reported that in term infants, the blood sugar levels decrease during the first 1-2 hours after birth, and the blood sugar's lower limit decrease to levels of 30-36 mg/dl in conditions of 3-6 hours of absence of nutrition (5, 6). This transient hypoglycemia is known to reach the adult blood sugar levels with a slow rise, at the 3rd -4th day of life (7). In a newborn term healthy infant in the first transition to extrauterine life, because the baby is seperated from the maternal source of the glucose, the blood sugar levels in the baby decrease significantly. The newborn can fix this hypoglycemia situation in a few hours after the birth without any intervention (7). In today's sicence, it is accepted that a significant lack of state of knowledge about this situation is present, why and how does the hypoglycemia develops exactly cannot be disclosed, however, it occurs physiologically as an adaptation to postnatal life.

In the recent years, it is suggested that the transient neonatal hypoglycemia is closely associated with congenital hyperinsulinism, and it is a variant of congenital hyperinsulinism (2). In glucokinase mutation activation, which is among the genetic causes of hyperinsulinemic hypoglycemia, the required threshold glucose level for the insulin release from the beta islet cells decrease, however in this mutation, a moderate level of hypoglycemia occurs and generally, the hypoglycemic brain injury is considerably at lower frequency compared to the other mutations. This also applies to hexokinase 1 (HK1) mutation. The presence of similar clinical and laboratory data in hyperinsulinemic hypoglycemic babies and glucokinase mutation activation suggest that the transient neonatal hypoglycemia might be as well a variant of this mutation.

The transient neonatal hypoglycemia in term healthy babies, is explained by the low glucose threshold in these babies, required for the insulin secretion (2). Another possible mechanism, is that it can be explained by insufficient suppression of the insulin and the normal levels of insulin, despite the hypoglycemia levels in most of the babies with a diagnosis of transient neonatal hypoglycemia.

Another theory is the extra insulin synthesis in the immature beta cells. In the rat experiments, the mRNA levels, which is synthesized by 2 different genes (membran piruvate/lactate carrieer: MCT1 ve lactate dehydrogenase: LDHa), which is not synthesized from the normal beta cells during hypoglycemia at the 1st and 28th days of life, was found to be 5-15 times higher at the 1st day (8). Today, MCT1 genetic mutation is known to cause hyperinsulinemia that is induced by exercise (9).

Another feature of transient asymptomatic hypoglycemia that needs to be explained is that it is unrelated to nutrition. It is reported that the blood glucose of a healthy full-term baby who was not fed for 8 hours following the delivery, is no different than a baby who was fed (10). In another study, where the similar results for the blood glucose levels were detected between the babies who were fed with colostrum, which includes very low calories and who were fed with baby formula, supports this data (11). However, the stimulating effect of colostrum on ketone metabolism should be noted (12). In the studies, it is reported that the blood glucose levels in the breastfeeded term babies are lower than the levels of babies fed with formula, and the ketone bodies are higher, and in case of breatfeeding, because the baby can use the ketone as energy, it may tolerate the lower glucose levels (12,13). Finally in the animal studies, it is shown that this stable hypoglycemia state cannot be exactly described with developmental disabilities of the neonatal hepatic glycogenolysis, gluconeogenesis or ketosis enzymes (2).

Although in the fetal life and neonatal early period, lactate and ketone bodies were shown to be able to be used as an alternative to glucose in the oxidative metabolism by the brain, the ability to use this feature in the babies is quite slow and in the form of a smooth transition. The situation in which some babies with the same low blood sugar levels stay asymptomatic, and some babies with the same blood sugar levels, hypoglycemia symptoms are present, is tried to be explained with this feature. In the studies related with ketone, in the case of transient hypoglycemia, the ketone and free fatty acid levels are found to be low in babies (2). In older children, it is known that ketones and fatty acids may be used for energy by brain, during hypoglycemia. The extremely low ketone levels in the newborn during the hypoglycemia in the first hours of life (it is about 10 times lower than it should be), renders the alterative energy pathways for the brain, useless. When assessing the blood glucose levels in the newborn, it would be the most appropriate approach to evaluate the ketone bodies, lactate and fatty acid levels, which are the alternative metabolic fuels for the brain (14).

The benefits of transient neonatal hypoglycemia;

The decrease in blood sugar enables the stimulation of the physiological processes to sustain life in the postnatal period.

The decrease in blood sugar stimulates appetite and rapidly stimulates the feeding cycle.

The decrease in blood sugar increases the oxidative lipid metabolism.

Clinical Symptoms of Hypoglycemia

It is reported that 30% of newborn have risk factor for hypoglycemia, 15% are diagnosed with hypoglycemia, and 10% are required admission to NICU (15). Hypoglycemia is clinically defined as a reduction of plasma glucose concentration to cause clinical symptoms and/or deterioration of brain functions. In the neonatal period, hypoglycemia doesn't have aspecific clinical finding, and it is generally detected in the screeing of blood sugar or

Table-1: Clinical findings of Hypoglycemia

Autonomic Dysfunctions	Shaking, jitteriness
	Sweating
	Tachypnea
	Paleness
Central Nervous System Dysfunction	Lethargy
	Stupor - Coma
	Convulsion
	Hypotonia
	Irritability
	Weak Cry or Aloud
	Decline in breastfeeding-unwillingness
Other Findings	Vomiting
	Cyatonic episodes of apnea
	Hypothermia
	Bradycardia

Table-2: Whipple's Triad In The Diagnosis of Hypoglycemia

1. Verification of low blood glucose levels with a reliable method
2. The clinical findings and symptoms to be chronic with hypoglycemia
3. Relief of clinical findings and symptoms when the glucose level is raised to normal values

incidentally in the laboratory tests. The frequently encountered clinical findings are presented in Table-1. However, all findings are not specific to hypoglycemia, and may be seen in many cases such as sepsis, and perinatal asphyxia. For the findings to be accepted as hypoglycemia symptoms, they must meet the criteria in Table-2, which are known as Whipple's Triad (16). The suspected hypoglycemia symptoms should be treated quickly without waiting for the laboratory results, due to their potential serious side effects.

Even though the hypoglycemia is defined as the detection of blood glucose levels below 2 standard deviation of the detected values in normal babies, it is accepted that this epidemiological definition is not appropriate to define neonatal hypoglycemia, because it is dependent to a wide variety of babies (hunger, satiety status), to the device that the blood sample is checked, and to the clinical experience of the person who draws blood.

Incidence of Hypoglycemia

It is reported that in the healthy singleton term babies, the frequency of detecting asymptomatic hypoglycemia (hypoglycemia limit: blood glucose <40 mg/dl) is 10%, the hypoglycemia episode develops in the first 24 hours in these babies, and the frequency of hypoglycemia in the first 1 hour of life in the babies who are fed with breastfeeding (7.8%) is significantly lower than the babies who are fed after the first hour of life (16.6%) (6). In this study, it is reported that in the baby who the mother gave birth to her first baby (23.1%), the hypoglycemia frequency is higher than the babies of multipara mothers (5.4%) (6). In a different study, it is reported that there is a significant increase in the frequency of hypoglycemia in the babies in whom the early breastfeeding support is delayed (17).

In a prospective hypoglycemia study with a large number of participants including 514 babies, it is reported that in 51% of newborn, the blood sugar levels decreased to below 47 mg/dl, which is accepted as the threshold value, and the blood sugar fell below 36 mg/dl in 19%, in 37%, the decrease developed after 3 normal values and in 6%, the first hypoglycemia attack developed after the first 24 hours of life (18).

Risk Factors For Hypoglycemia

- **The infant of a diabetic mother** (mother with gestational diabetes, type 1 or type 2 diabetes)
- **İntrauterine growth restriction (IUGR)**
- **SGA**
- **LGA:** In a study, LGA births were reported as not a risk a factor, and in these babies, there is no need for screening (19). However AAP (American Academy of Pediatrics) reports that the presence of prediabetes in the mother, which lies under the pathophysiology of being LGA can never be ruled out, so, this is a risk factor in developing hypoglycemia in these babies (20).
- **Prematurity**
- **Maternal Risk Factors:** Obese mother, preeclampsia-eclampsia or hypertension, presence of fever at birth, giving high glucose fluid to mother at birth, maternal use of beta-blockers or hypoglycemic medication (12). Having family history of hypoglycemia disease.
- **Risk Factors Related To The Baby:** They can be listed as postmaturity, babies whom are required NICU, meconium aspiration syndrome, respiratory failure symptoms, polycythemia, multiple pregnancy, birth asphyxia, Beckwith-Weidemann Syndrome, midline defects syndromes, erythroblastosis fetalis, improper insertion of the umbilical artery catheters (1,12). Meconium stained with amniotic fluid is not a risk factor for hypoglycemia (21). The presence of perinatal stress may cause the hypoglycemia by

hyperinsulinemic hypoglycemia to last for several weeks (2). The extremely low blood sugar levels in the first day of life can be accepted largely as a reflection of peripartum factors.

The Infant of Diabetic Mother

The incidence of hypoglycemia episode in the infants of diabetic mothers is 40% higher than in non-diabetic mothers. It is associated with neurological problems in the advanced stages, with a significant increase in the frequency of convulsion, coma and death (22). Hypoglycemia is usually detected in the first 4 days of life in the infants of the diabetic mothers, but it may insist until the first week (22).

There is no consensus on when to check the blood sugar in the infants of diabetic mothers. It is recommended to check the blood sugar levels at 30th minute, 1st, 2nd, 4th, 8th and 12th hours after birth and at the time when a hypoglycemia symptom is detected in the infants of diabetic mothers (23). In the infants of insulin-dependent mothers, it is also recommended to check it at 1st, 2nd, 3rd, 6th and 12th hours (24). Again in these babies, the blood sugar chould be checked at 30 minutes after the beginning of glucose infusion or after the time that the glucose dosage is changed (25). It should be noted that if the blood sugar control from the umbilical cord after birth is determined high, secondary severe hypoglycemia may develop to hyperinsulinemia. In the studies performed with the infants of diabetic mothers, in the case of glyburide or insulin use during pregnancy, the incidence of hypoglycemia in the first hour of life is reported to increase significantly, and in the infants of mothers which control their blood sugar with only diet, hypoglycemia is reported to be at normal incidence (26).

It is reported that in mothers with gestational diabetes, when the body mass index is over 25 kg/m^2, the hypoglycemia risk in infants increases independent from the blood sugar levels (27). Again in the pregnancies with gestational diabetes, the male infant gender is detected to be an independent risk factor for hypoglycemia (28). A recently published study reports that a sedentary life of the mother in the 24 hours before the delivery and a high-calorie diet, increase the risk of hypoglycemia in the infant at a high rate (29).

A Numerical Value Determination As The Definition of Hypoglycemia

Today, there is no numeric value that is based on evidence that could be considered as the threshold of hypoglycemia. Many authors define many different glucose levels as hypoglycemia, however this led a complicated situation. As well as the different gestational weeks of the newborn, the symptoms of hypoglycemia seen in an extend period of time (in the first 10 days), may have contributed to these differences in the values. In different studies it was reported that in the first 3 days of life, the blood sugar level being below 20 mg/dl in preterm babies, and below 30 mg/dl in term babies, and in all age groups, being below 40 mg/dl exist in the literature (4,30). After Lucas et al. (31) detected that in recurrent and asymptomatic hypoglycemia in the infants with values below 47 mg/dl, the motor and cognitive development is seriously affected, the numerical limit for hypoglycemia is widely accepted as below 47 mg/dl today. In the first 10 years of life, in a large study in which the babies with below 47 mg/dl levels of blood glucose for at least 3 times and the babies with no values below 47 mg/dl was detected, were compared, in the 15th years of life of these babies, no difference was detected between the psychometric, intelligence, numerical ability and state of behaviour (32). This situation shows that value of 47 mg/dl being accepted as the threshold is not completely accurate. In different studies in the hospitalized patients; values below 30.6 mg/dl in term infants, and below 19.8 mg/dl in preterm and SGA infants were accepted as the borderline for hypoglycemia (1). The limit value for the intervention to raise the blood sugar may be accepted as the blood sugar value to be <36 mg/dl in 2 consecutive measurements, or <18 mg/dl in a single measurement (33).

It is reported that in adults and older children, the level of blood glucose level at which the brain functions are impaired (definition of neuroglycopenia)

is about 50 mg/dl, however at neonatal period, no threshold value has been fully determined (34). After the first 72 hours of life, in all newborns, the blood sugar should be kept over the value 70 mg/dl (35). Due to the wide difference in the clinical studies, many authors emphasize that the path to follow in this situation is to form a protocol in the working section on hypoglycemia practices and to follow babies on this protocol.

AAP (American Academy of Pediatrics) published a protocol relating to the monitoring of glucose levels in infants after birth in 2011 (20). It should be kept in mind that this protocol is only applicable to late preterm infants (34-36 $^{6/7}$ weeks), SGA, LGA and infants of diabetic mothers, not in healthy term infants and in the presence of an underlying disease (sepsis, asphyxia, etc.). The recommendation of AAP is presented in Table-3.

biases. Due to high incidence of deviation of the measurement method and incorrect measurements, all blood sugar levels detected at the border or at low values, must be checked with the laboratory measurements. Anemia causes to measure the glucose levels higher than it is, and polycythemia to be lower than it is (5).

The other reasons that may cause measurement errors in glucometers:

Blood galactose level > 15 mg/dl

Hyperlipidemia (triglycerides >1800 mg/dl)

Blood ascorbic acid > 3mg/dl, cause high blood sugar measurement results.

2.Blood gas analyzer (point of care: POC):

Although fast and enzymatic measurement of blood sugar technique, because it uses the blood gas analyzer device, it seems rather to be expensive. In practice, it is not widely used.

Table-3: The recommendations for monitoring and treatment of AAP (American Academy of Pediatrics) in postnatal glucose homeostasis in late preterm, term and SGA, DAB/LGA infants

LATE PRETERM (34-36 $^{6/7}$ WEEKS) and SGA (screening at 0-24 hours), IDM, LGA ≥34 weeks (screening at 0-12 hours)			
SYMPTOMATIC and < 40 mg/dl → IV glucose			
ASYMPTOMATIC			
THE FIRST 4 HOURS OF LIFE FIRST FEEDING IN 1 HOUR Check the blood sugar in 30 minutes after the first feeding		**THE FIRST 4-24 HOURS OF LIFE A continuous feeding at every 2 - 3 hours will be provided Check the blood sugar before each feeding**	
First blood sugar < 25 mg/dl		**Blood sugar < 35 mg/dl**	
Feed and check in 1 hour		**Feed and check in 1 hour**	
< 25 mg/dl ↓ IV glucose	**25 - 40 mg/dl ↓ Refeed /if needed IV glucose**	**< 35 mg/dl ↓ IV glucose**	**35 - 45 mg/dl ↓ Refeed /if needed IV glucose**

IDM: Infant of Diabetic Mother, IV: Intravenous, SGA: Small for Gestational Age, LGA: Large for Gestational Age

How To Measure The Blood Sugar

1. Glucometer:

It is a device to measure the blood sugar with a strip at patient's bedside. This method provides a practical, easy use with its fast results and being able to be used at patient bed. A disadvantage of bedside glucometers is that especially at low blood glucose levels, it may show a ±10-20 mg/dl of

3.Continuous glucose measurement method (Continuous glucose monitoring sensors: CGMS):

Its use is defined as interstitial glucose measurement method in a study. In the study, when it is compared with capillary blood glucose; in 25% of patients the interstitial blood sugar was detected as low, while in capillary blood sugar, this situation couldn't be detected (36). In the same study, when the below 47 mg/dl level was taken as the limit for hypoglycemia

in measurement with CGMS, it was detected to be not effective in showing the neurosensorial disorders in infants with hypoglycemia. Thus, no difference has been detected in hypoglycemia present and absent groups when the target was taken as below 47 mg/dl with this measurement method in terms of neurosensorial development (36). Today, there is not enough information related with the effectiveness and awareness of useness of this measurement method (27).

4.Laboratory enzymatic method:

This method is accepted as the most accurate method, however its biggest disadvantage is that it cannot be used bedside and the result cannot be gained fast enough. It allows to measure directly the plasma blood sugar with glucose oxidase, hexokinase or dehydrogenase methods. All borderline or low levels determined by glucometer should be controlled by this method. Because plasma is used in this method, the values are expected to be about 10% higher than values with glucometer. However, until the delivery to the laboratory, the reduction of the blood sugar by 6-8 mg/dl/hour with glycolysis by the red blood cell mass in full blood should be considered. To prevent this reduction, fluoride containing tubes which inhibit the glycolytic pathway may be used.

5. Noninvasive glucose measurement:

Today, studies related with the peripheral glucose measurement with infrared technology is continuing, while there is no non-invasive method accepted.

When To Test The Blood Sugar:

- **Every baby's potential risk factors should be determined and when to test the blood sugar and at which intervals to monitor the baby should be decided.**
- **In healthy term babies with no risk factors, the testing blood sugar is not routinely recommended.**
- **To check the hypoglycemia in all babies as screening would cause an increase in the unnecessarily mother and baby seperation, and will therefore have a negative effect on the breastfeeding policy.**

In the infants of diabetic mothers, asymptomatic hypoglycemia develops in the first hour of life, and this period usually may extend to the first 12 hours (37). In the studies, the blood sugar is recommended to be checked immediately after birth, at 30th minute, at 1st, 2nd, 4th, 8th and 12th hours and at detection of hypoglycemia symptom in infants of diabetic mothers (23).

In SGA babies, low blood sugar development starts earliest at the 3rd hour, and this period may extend to 10th day from birth (38). In late preterm and SGA babies, the blood sugar should be checked at 1 hour from birth, and at the first 24 hour of life, before all feedings of 2-3 hours (20).

It is reported that in 40% of SGA babies, a low glucose concentration is present and at about half of these babies, there is hyperinsulinemia (39). In some of the hypoglycemias in SGA babies, no increased insulin values, and low B-hydroxybutyrate, which is a ketone body and free fatty acid values, with an inappropriate insulin value rise, were detected (40).

Neuroendocrine Response to Hypoglycemia

The hormonal response in a hypoglycemic baby initially develops as the decrease in the insulin secretion, followed by an increase in the glucagon level. Subsequently with sympatho-adrenal discharge, the epinephrine levels increase. When the hypoglycemia continues, cortisol and growth hormone release is increasingly engaged. In adults and older children, the blood sugar threshold is accepted as 55-65 mg/dl for the neuroendocrine response (4). No threshold value is known for the early neonatal period after birth.

When the hormonal status of transient hypoglycemia has been investigated, when both term and preterm infants were stimulated with epinephrine, or given glucagon, a significant increase in their blood sugar was detected. It is thought that the glycogen reserves in the infant liver cannot be used even there is hypoglycemia, and insulin is thought to block this effect.

According to the pediatric endocrine society: the brain's use of glucose starts to be limited when the plasma glucose levels become 55-65 mg/dl.

Neurogenic symptoms are seen when the plasma glucose is <55 mg/dl, and the deterioration in cognitive functions (neuroglycopenia) is seen when plasma glucose is <50 mg/dl (41).

Hypoglycemia and Neurological Damage

Neonatal hypoglycemia is a frequent situation and neurological damage can be prevented with convenient treatment. In cases where hypoglycemia is recurrent and persistently in low levels, even its relation with neuromotor damage in babies has been clearly shown, no significant relationship with especially asymptomatic hypoglycemia attacks and poor neuromotor development or brain damage could be proven today (6,36). It is not possible that one hypoglycemia value may cause brain damage (41). The duration of hypoglycemia and its degree are important factors in this case. In a different study, the stress that is induced by pain in a newborn (to get blood with a strip) itself is reported to have negative effect on brain development (42). The most frightening data of hypoglycemia is; in cases with symptomatic resistant hypoglycemia, in 18-month cranial MRI findings, 95% of irreversible wihte matter damage is detected (43).

Bayley III social-emotional score was reported to be signficiantly better in infants with neonatal hypoglycemia (104±15) than infants without hypoglycemia (100±14), and in other Bayley III scores no difference has been reported (36). In contrast to hypoglycemia, hyperglycemia is reported to have negative effect on neurodevelopment in infants with low birth weight (44). The studies emphasize that to increase the blood sugar quickly and in high rates when planning the treatment of suspected hypoglycemia may have negative effect on neuromotor development.

The relation of the effect of the amount of blood glucose on brain functions, the changes in the somatosensory evoked potentials and the changes in the cerebral blood flow were evaluated, but no clear view has been reached (4). In 2 studies the evoked somatosensory potentials and the incidence of developmental delay have been reported to increase in infants with blood glucose concentrations of below 47 mg/dl (45,46). Because of these two studies, despite the absence of sufficient evidence on the effectiveness or safety of the threshold value 47 mg/dl, many researcher embraced it as the borderline for the treatment of hypoglycemia in newborn. Indeed, in a 2-year prospective follow-up study consisting 404 babies that accepts the hypoglycemia blood sugar limit as 47 mg/dl, the babies with hypoglycemia were reported to have no significant side effects on the neurological development, compared to babies without hypoglycemia (36).

Persistent Hypoglycemia

It may be defined as the hypoglycemia that persists after the first 48-72 hours of life. The main causes:

1. The insufficiency of glycogen storage

Prematurity

Intrauterine growth restriction (IUGR)

2.Glucose reproduction disorders

a-Metabolic disease

Glycogenolysis (Glycogen storage disorders)

Gluconeogenesis (Fructose 1-6 bisphosphatase, pyruvate carboxylase deficiency)

b-Endocrine diseases

Primary pituitary and adrenal gland insufficiencies: Cortisol or growth hormone deficiencies

c. Other causes

The maternal betamimetics use: it blocks the effect of epinephrine in glycogenolysis.

Hypothermia

Severe liver failure (asphyxia, etc.)

3. The increase in glucose utilization rate

With hyperinsulinemia

Persistent hyperinsulinemic hypoglycemia (the incidence in the group 25-50%)

IUGR

Beckwith-Wiedemann Syndrome

Perinatal asphyxia-stress

Giving the mother liquids containing high glucose levels during birth or use of antihyperglycemic drug

(sulfonylurea)

Placing the umbilical catheter inappropriately around celiac artery

Exogenous insulin use

Neonatal diseases that increase insulin secretion: alloimmune hemolytic diseases, meconium aspiration syndrome, hypothermia and polycythemia.

Without hyperinsulinemia

Asymmetric SGA

Disruption of tissue perfusion, heart failure

Perinatal asphyxia

Polycythemia

Sepsis

To differentiate these diseases from transient neonatal hypoglycemia in the first 48 hours is impossible. However, early diagnosis and treatment in these diseases significantly reduce the persistent brain damage and the development of sequelae (47). Therefore, further investigation is recommended in babies with a high rate to be diagnosed with persistent hypoglycemia after 48 hours (41).

Genetic Hyperinsulinemia

With the advancing molecular diagnostic methods, mutations are defined for an important portion of resistant hypoglycemias. Now we are able to have an idea about the prognosis of the patient based on the genetic results. The gene mutations seen frequently at chromosome 11p14-15 region: K_{ATP} mutations (ABCC8: SUR1 and KCNJ11: Kir6.2), HNF4A, HNF1A, HADH, HK1 gene mutations. Besides, GLUD1, HADH, HNF4A, HNF1A VE UCP2 gene mutations are known to cause hypoglycemia that response to diazoxide treatment, GCK and recessive K_{ATP} mutations are known to cause hypoglycemia refractory to diazoxide treatment. Dominant mutations in K_{ATP} may be both refractory and sensitive to diazoxide (27). ALDH7A1 mutation: causes pyridoxine-dependent epilepsy and hyperinsulinemic neonatal hypoglycemia.

The liquid treatment used in hyperinsulinemic hypoglycemia (HH) is generally high. Therefore to reduce the fluid overload, hydrochlorothiazide is used as a diuretic, which additionally increases the excretion of potassium. It is necessary to evaluate the cardiac functions of babies with HH, with ECO and ECG. In the studies, the simultaneous incidence of HH and hypertrophic cardiomyopathy has been detected to be high (48,49).

Identifying Location In Pancreas

If surgical treatment for hyperinsulinemia will be performed, standard imaging techniques remain totally inadequate to detect the diffuse involvement and local involvement. The mutation types detected in genetic tests provide limited information about diffuse or local involvement of pancreas, however, for a complete distinction, 18-Fluoro-L-DOPA positron emission tomography (PET), which has a high sensitivity and specifity, should be performed (it ensures the local involvement 100% preoperatively) (50). Intraoperative ultrasound or intraoperative venous insulin sampling in cases which PET cannot be performed, are the alternative ways that can be applied.

Treatment Of Neonatal Hypoglycemia

The treatment of hypoglycemia is focused on 4 main purposes:

1.The improvement of blood glucose levels in symptomatic patients

2.The prevention of symptomatic hypoglycemia in patients at risk

3.The prevention of unnecessary interventions in infants that would improve spontaneously

4.Early identification of patients with underlying severe hypoglycemic disease

Primarily protective measures should be taken to prevent the development of hypoglycemia, and breastfeeding should be supported and increased. Feeding the baby with formula must be kept in mind, may cause stress on the mother as the breast milk would be insufficient and and as she is insufficient of feeding her baby (12). The blood sugar levels of 20-39 mg/dl indicate a requirement of feeding with formula, and levels of ≤19 mg/dl indicate requirement of IV dextrose support (12). The primary treatment in babies who have

asymptomatic or incidentally detected hypoglycemia, is to provide nutrition by oral route. The early breastfeeding support in the first hour of life is defined as a proactive treatment, that it prevents hypoglycemia and treats it, and this situation is indicated in the AAP guideline (20). Baby nutrition should be provided in the first hour, and the blood glucose levels should be tested 20-30 minutes after feeding. Formula feeding should be done when there is insufficient breastfeeding. There is only one study on dextrose gel application on the cheek to reduce hypoglycemia development in babies with risk, and no sufficient knowledge is available about this procedure to be routine (51).

If hypoglycemia limit values (Table-3) can be exceeded by oral feeding, the baby is feeded with 2-3 hours of intervals, and the blood sugar is tested before feeding in this case. If the blood glucose doesn't increase to the desired levels after feeding, IV dextrose support is given. In the presence of hypoglycemia symptoms, or the blood sugar levels not to be able to be above 45 mg/dl with 3 feedings, IV fluid support should be given.

In a study performed about feeding with breast milk and the follow-up of hypoglycemia; when the health workers are trained, it is known that the incidence of formula feeding in babies reduces, the breastfeeding incidence increases, the hospitalization rates of babies decrease and the need for treatment with IV fluid decrease significantly (12). This study emphasizes that more nursing care time is needed to prevent neonatal hypoglycemia (12).

Although AAP society published a guideline about hypoglycemia in 2011, a study should be performed for the functioning of each unit, and each unit must establish a protocol for itself that is performable.

The targeted blood glucose levels in the treatment of hypoglycemia:

The blood glucose levels in babies who are treated for hypoglycemia are targeted to be;

>50 mg/dl in the first 48 hours of life

>60 mg/dl after 48 hours of life

>70 mg/dl in the babies who were diagnosed with hypoglycemia disease (35).

When to send the baby home- discharge:

In the cases of the blood glucose level to be > 50 mg/dl before feeding for 3 times in the first 48 hours of life with enteral feeding; and after 48 hours, to be >60 mg/dl, the baby can be discharged (2).

Treatment of resistant hypoglycemia

Hypoglycemia detected after the 48th hour of life, or the state of still needing parenteral glucose support after the 48th hour of life.

When to do further investigation in resistant hypoglycemia?

The tests for resistant hypoglycemia should be performed when the blood glucose levels are <50 mg/dl in plasma, or <40 mg/dl with glucometer. If the blood glucose levels are above these levels with support, the decrease in the blood glucose levels may be planned with close follow-up of the baby at 6-8 hours of fasting or making a decrease in the IV dextrose support. This situation should be closely monitored and when the desired value is reached, it should be terminated immediately.

Further investigations in the first step: Plasma insulin, Beta-hydroxybutyrate, blood gas pH, bicarbonate, lactate and free fatty acids are measured.

Second step: Plasma C peptide, growth hormone, cortisol, thyroid hormone, acylcarnitine profile, plasma free and total carnitine, serum amino acids, urine organic acids and specific gene analyses are performed.

- **Dextrose IV fluid**

In symptomatic hypoglycemia: At the presence of symptoms in the treatment of hypoglycemia, intravenous (IV) 2-5 ml/kg (min. 200 mg/kg), %10 dextrose bolus to go in 5 minutes, 6-8 mg/kg/minute glucose infusion is initiated, the blood glucose level is tried to be kept above 45 mg/dl, if the desired effect cannot be achieved, the infusion rate of glucose is increased at 2 mg/kg/minute rate (35). If the blood glucose level cannot come to the desired level with 12 mg/kg/minute despite infusion, evaluation for medical treatment and central venous catheter should be performed. After 20 minutes from bolus, the blood glucose levels should be checked.

If the levels are below the desired levels in

asymptomatic hypoglycemia, enteral feeding is performed, if with enteral feeding, the desired level cannot be achieved, or the baby is not able to be fed by enteral feeding, 4-6 mg/kg/minute dextrose is initiated. After a study that showing an increase in the neurological damage with raising the blood sugar quickly in asymptomatic babies, bolus is not recommended in asymptomatic babies, even at the presence of low blood sugar (1,35).

Because the amount of fluid in babies that require IV fluid treatment, cannot be more intense than 12.5% in concentration, some infants may achieve more fluid than the maintenance values. In practice, these babies should be closely monitored for fluid overload and the use of diuretics should be added to the treatment in appropriate babies.

- **Glucagon**

It is performed if the blood glucose is <50 mg/dl despite the continuous maximum dextrose (10-40 mg/kg/minute) fluid. In the case of blood sugar to be <60 mg/dl after the 48th hour of life, it can be given IV or subcutaneously. Thus, in symptomatic hypoglycemias where the vascular access cannot be gained. The response to glucagon is gained in 15-30 minutes. The blood glucose increases about 30-50 mg/dl. Dose: 20-30 microgram/kg/hour IV infusion or subcutaneously, maximum dose: 1 mg/24 hour.

- **Glucocorticoid**

Its use is not recommended except infants with surrenal insuficiency. If it is going to be used, 1-2 days for a short period, 2-6 mg/kg hydrocortisone oral or IV may be used. It acts through the stimuation of gluconeogenesis by cortisone and lowering the glucose utilization in peripheral tissues. The serum cortisone and insulin levels should be certainly checked before administration.

- **Diazoxide**

It is the first step in treating hyperinsulinemia. It acts by binding to the sulphonylurea receptors at beta islet cells, and with this binding it stimulates K_{ATP} channel as an agoinst, which blocks the insulin secretion in the cell. Its effect starts 1 hour after the administration. Its dose is 10-15 mg/kg/day, given in 2-3 divided doses. Its initial dose is 5 mg/kg/day, and maximum dose is 20 mg/kg/day. It is initiated with low doses, and the dose in increased if no response is achieved; in different protocols, it is initiated with maximum doses, and when the response is achieved, it is tapered. If the effect of the drug is not detected within 48 hours, alternative medical drugs should be considered.

- **Octreotide**

It is a somatostatin analogue. It is used as a second choice in patients unresponsive to diazoxide. It inhibits the insulin secretion. It has a short term effect. Dose of 5-20 mcg/kg/day, subcutaneous injection, given in 2-3 doses is administered. Its maximum dose is unknown. In long-term treatment, IM long-acting octreotide monthly may be administered. However, no adequate knowledge about its activity is not fully available. Because it suppresses the growth hormone in long-term use, the growth and development should be closely monitored.

- **Nifedipine**

It's a calcium channel blocker. It regulates the insulin secretion. Dose of 0,5-2 mg/kg/day, may be added to the other drugs.

- **Sirolimus**

mTOR (mammalian target of rapamycin complex) pathway which provides beta cell proliferation, is known to be induced with genetic mutations of hyperinsulinemia and causes to cell proliferation. Sirolimus inhibits the beta cell proliferation as mTOR inhibitor. It is reported to be used before surgery in cases resistant to diazoxide and octreotide (52,53). This drug which is an Immunosuppressive is initiated as 0.5 mg/squaremeter, the drug blood levels are tried to be kept between 5-15 ng/mL and checked every 5 days.

- **Surgical treatment**

It should be considered in cases that cannot be controlled by medical treatment, and no response despite 6-8 week of treatment. The pancreas is subtotally-near totally resected in a rate of 95-99%. The family members should be informed on that pancreatectomy may cause insulin-dependent diabetes in short-term, and malabsorbtion and growth and development retardation in long-term. It should be noted that these babies should be monitored for exocrine pancreatic insufficiency and should be supported with pancreatic enzyme replacement when necessary.

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