

Management Approach to Hypoglycemia

Miriam Ciljakova, Milos Jesenak,
Miroslava Brndiarova and Peter Banovcin
*Pediatric Department of University Hospital and Jessenius
Medical Faculty of Comenius University, Martin
Slovakia*

1. Introduction

Management of hypoglycemia in children and adults depends on many factors. The most important point of view is the level of hypoglycemia and the relevance of clinical symptoms. In the case of severe hypoglycemia, all effort must be used to maintain euglycemia as soon as possible. However, the appropriate therapeutic approach relies on correct diagnostic evaluation. In relation to the age of onset, different causes of hypoglycemia should be considered in neonates, infants, children and adults.

The risk of hypoglycemia is declining during the life, low blood glucose level is the frequent problem, mainly in neonatal period. The majority of neonatal hypoglycemia are due to problems with the normal processes of metabolic adaptation after birth, and strategies enhance the physiologic transition should help prevent such episodes. Further investigation and specific intervention should be considered when hypoglycemia is unusual in severity, duration, or occurs in an otherwise low-risk infant (Desphande & Platt, 2005).

Important factor for diagnosis is timing of hypoglycemia in relation to fasting. If hypoglycemia occurred in a short period after meal (2-3 hours) and after overnight fasting, hyperinsulinism would be assumed. Low blood glucose level within 4-6 hours after ingestion is typical for defect in glycogenolysis. If hypoglycemia occurs more than 6 hours after feeding, disorders of fatty acid oxidation or defect in gluconeogenesis are supposed (de Leon et al, 2008). In older patients, the fasting period inducing hypoglycemia is usually longer.

Physical examination can also be helpful in diagnostic evaluation. The presence of central cleft lip (or palate), micropenis and undescended testes in male neonate strongly suggests the occurrence of hypoglycemia due to pituitary hormone deficiency. If TSH deficiency was associated, untreated infants would suffer from psychomotoric retardation, growth retardation is typical later at the age 2-3. Large for age newborns with recurrent hypoglycemia could be suspected of autosomal recessive form of hyperinsulinism, if mother did not suffer from diabetes in pregnancy. Short stature and hepatomegaly is a part of clinical picture of glycogen storage disease type 1 (Langdon et al, 2008).

Hypoglycemia is expected in a risk group of neonates (e.g. premature, small for age) and in diabetic patients. If etiopathogenesis of low blood glucose level is unknown and unexpected, the sampling of blood and urine at the time of hypoglycemia is crucial (critical sample). In diagnostic algorithm, it is necessary to measure plasma substrates: ketones (aminoacetate and hydroxybutyrate acids), lactate, free fatty acids, ammonia level, and

hormones: insulin, C-peptide, cortisol, growth hormone at the time of low blood glucose level. Hypothyroidism ought to be excluded in all patients with low blood glucose level. If hypoglycemia was less than 2,8 mmol/l (50 mg/dl), repeated sampling and measurement of counter-regulatory hormones, such as cortisol and growth hormone, would be suggested 30 minutes after low blood glucose concentration. At the blood glucose level of 2,2 mmol/l and less, the peak values of cortisol and growth hormone are reached in half an hour, and are comparable to those in insulin stimulation test (Weintrob et al, 1998).

At the time of hypoglycemia, the lack of ketones makes pediatric frequent diagnosis of ketotic hypoglycemia nonprobable. Ketoacidosis is also common in cortisol deficiency, whereas lactic acidosis is part of disorders of gluconeogenesis like as glucose 6-phosphatase deficiency. Ketones and lactate are the alternative fuel for brain, disorders with high plasma level of these substrates are linked with laboratory serious hypoglycemia without clinical symptoms of neuroglycopenia. Some patients may have only few symptoms at plasma glucose level as low as 1,1-1,7 mmol/l (20-30 mg/dl). On the other hand, in defects of ketogenesis, signs may begin to appear at plasma glucose level of 3,3 mmol/l (60 mg/dl) during fasting. The average cut point of plasma glucose level to provoke clinical adrenergic and neuroglycopenic symptoms is 2,8 mmol/l (De Leon et al, 2008).

High level of free fatty acids with hypoglycemia is a part of defects of fatty acid oxidation associated with coma, hepatocellular failure and hyperammonemia (Reye-like syndrome). Valproic acid can block β -oxidation, treatment of epilepsy may provoke Reye-like syndrome in some patients. Early supplementation with carnitine and riboflavin, avoidance of fasting and low-fat diet can be useful and lifesaving. Acyl-carnitine profile of blood spots in newborn screening is able to detect most fatty acid oxidation disorders. Free fatty acids do not pass blood-brain barrier and can not be used as a energy substrate in brain.

Hypoglycemic symptoms follow usually the same pattern for each patient. Especially in type 1 diabetes, it is important to teach patient and all family members how to recognize and treat hypoglycemia in a safe and effective manner as soon as possible. Coffee and cola caffeine may cause symptoms of hypoglycemia at a slightly higher blood glucose level than usually. The fact that caffeine enhances the intensity of symptoms warning hypoglycemia may be useful for patients with „hypoglycemia unawareness“. On the other hand, treatment of high blood pressure with β -blockers may have opposite effect and makes symptoms of hypoglycemia less obvious. Patients with diabetes on β -blockers treatment should check blood glucose level in case of sweating without any reason. It may be the only sign of a very low blood glucose. Similarly, few symptoms are noticed in diabetics treating for depression with SSRIs, patients may suffer from hypoglycemia unawareness, too (Hanas, 2004).

The warning adrenergic symptoms precede typically neuroglycopenic ones and work as a brain protection. Diabetes mellitus may be associated with autonomic dysfunction, warning symptoms are being lost and hypoglycemia becomes unawareness. Frequent hypoglycemia may cause lowering of threshold for triggering adrenergic signs that start commonly at the blood glucose level 3,3-3,6 mmol/l (60-65 mg/dl) in diabetic patients. On the opposite side, if the average glycemia was 15 mmol/l within a week, the warning symptoms could start at the blood glucose level 4,5-5,5 mmol/l (80-100 mg/dl). Neuroglycopenic signs are mostly independent on the recent blood glucose values, observed in glycemia below 2,8 mmol/l (Hanas, 2004).

For correct management of patients with hypoglycemia, two glucose thresholds must be distinguished. The first one is diagnostic glucose level, hypoglycemia is usually considered in

the case of plasma glucose value below 2,8 mmol/l. Such glucose concentration is helpful for immediate sampling of alternative fuels and hormones, and consequently for differential diagnosis of hypoglycemic patients. The second one is therapeutic glucose value, the goal of appropriate treatment of hypoglycemia is to maintain plasma glucose within normal range 3,9-5,5 mmol/l (70-100 ng/ml) (Langdon et al, 2008).

The glucose level can be measured as whole blood glucose or plasma glucose. Plasma glucose is approximately 11% higher than whole blood glucose. Methods of measuring glucose level with bedside glucose meters were originally designed for diabetes management. These monitors are adequate for management of hypoglycemia, but are not accurate enough for measurement of hypoglycemic level. Latest development in bedside monitoring has improved the technology, but is not sufficiently accurate and precise to establish a diagnosis of hypoglycaemia. As a screening test it may be useful, any meter blood glucose level less than 3,3 mmol/l should be confirmed by more precise laboratory measurement of whole blood or plasma glucose concentration (Gamma et al, 2000).

Blood samples that are not processed promptly can have erroneously low glucose levels, as a result of glycolysis by red and white blood cells. At room temperature, the decline of whole-blood glucose can be 0,3-0,4 mmol/l/hr (5 to 7 mg/dl/hr). The use of inhibitors, such as fluoride, in collection tubes prevents this problem. Falsely low (or high) glucose values may occur with samples drawn from indwelling lines without adequate flushing of the saline (or glucose) infusate (de Leon et al, 2008).

2. Management of hypoglycemia in neonates and infants

Traditionally, lower standards for hypoglycemia were accepted in neonates. The major reason was statistical, low blood glucose is so common in neonatal period that it must be taken as a normal. Recently, the same definition and the same targets for treatment of hypoglycemia have been recommended in neonates and in older patients (de Leon et al, 2008). Moreover, the consequences of delayed diagnosis or inadequate management may be more harmful to a developing brain in neonates and infants (Menni et al, 2001).

Previously, the blood glucose concentration at which clinical signs occurred were used to define hypoglycemia. These signs, such as changes in level of alertness and tone, apnoe, tremors or seizures are not specific in neonates and infants. In the first few hours, after birth fuels apart from glucose are also relevant in providing brain energy. Therefore the presence or absence of clinical signs can not be used to differ between normal and abnormal glucose levels, although decreased level of consciousness or seizures should always suggest the possibility of hypoglycemia (Desphande & Platt, 2005).

The cerebral fuel economy depends on blood glucose level, the availability of alternative fuels such as ketones and lactate, the local adaptation of microcirculation, the interaction with other brain cells and the concurrent neonatal condition such as hypoxia and sepsis (Salhab et al, 2004). The immediate consequence of transition from fetal to neonatal life is the interruption of continuous glucose supplies. After birth, there is a rapid fall in blood glucose level, reaching a nadir between 1-2 hr in healthy term infants as well. Such low blood glucose level is usually accompanied by ketogenic response, particularly in breast-fed infants. Ketones provides alternative fuel for brain and prevents the neonate to become symptomatic. Even in the absence of any nutritional intake, the blood glucose rises significantly within 3 hrs due to counter-regulatory hormone response. Therefore, healthy asymptomatic neonates are proposed to avoid the blood glucose measurement during the

first 2-3 hrs after birth and only glycemia less than 2,0 mmol/l requires other intervention (Desphande & Platt, 2005). However, up to 10% of normal term neonates are not able to maintain plasma glucose concentrations above 1,7 mmol/l (30 mg/dl), if their first feeding is delayed for 6 hrs after birth (Lindley & Dunne, 2005). In case of this late first feeding, glycemia above 2,8 mmol/l (50 mg/dl) has been observed only in two thirds of healthy neonates. Promotion of first feeding soon after delivery is the basic approach to prevention of such blood glucose declining.

Some common maternal or neonatal problems expose a baby at risk of significant hypoglycemia (Table 1). Often measurements of blood glucose are helpful, even though in asymptomatic risk neonates. Severely intrauterine growth retarded (IUGR) neonates may have low cord blood glucose concentrations due to intrauterine hypoglycemia. On the other hand, hypoglycemia should be excluded in all clinically unwell infants. Clinical signs of common neonatal illnesses are shared by those with hypoglycemia. Moreover, many neonatal disorders can lead to hypoglycemia (Desphande & Platt, 2005).

Blood glucose concentrations show a cyclic response to an enteral feeding, reaching a peak approximately one hour after meal and a nadir just before the next feeding. In risk neonates, initial blood glucose measurement, immediately before the second feeding, may detect the most babies who can not manage adequately glucose homeostasis. Once or twice a day pre-feeding blood glucose determination may be sufficient in stable neonates, since the clinical condition has not been changed or the previous volume of milk has not been restricted. Laboratory standard blood glucose measurement is reliable and preferable to inaccurate reagent strip-based estimations (de Rooy & Hawdon, 2002).

Maternal conditions	<ul style="list-style-type: none"> • Diabetes (pregestational and gestational) • Drug treatment (β - blockers, oral hypoglycemic agents) • Intrapartum glucose administration
Neonatal problems	<ul style="list-style-type: none"> • Preterm • Intrauterine growth restriction • Perinatal hypoxia - ischemia • Hypothermia • Infection • Polycythemia • Infants on parenteral nutrition • Obvious syndromes (e.g. midline defects, Beckwith - Wiedemann syndrome)

Table 1. „At - risk“ infants who require monitoring of blood glucose concentrations (Desphande & Platt, 2005).

The most common neonatal hypoglycemia is due to delay of normal metabolic adaptation after birth. Occasionally, especially in IUGR neonates, a period of a week or more with high intravenous glucose infusion rate may be required. Blood glucose concentration often falls down in perinatal asphyxia, polycythemia, sepsis and with maternal use of β -blockers. Rarely, hypoglycemia is the presenting symptom of hormonal disorders or inborn errors of metabolism, such as hyperinsulinism (Yap et al, 2004), hypopituitarism and fatty acid oxidation disorder. Some clues can make hormonal or metabolic disorder very suspected:

- Family history of sudden infant death, Reye-like syndrome, or developmental delay
- Healthy, appropriate for gestational age, term infant with symptomatic hypoglycemia
- Hypoglycemia with midline defects, micropenis, exomphalos
- Hypoglycemia with seizures or abnormalities of consciousness
- Persistent or recurrent hypoglycemia
- Glucose infusion rate more than 10 mg/kg/min

Sample	Investigations
Blood	<ul style="list-style-type: none"> • Intermediary metabolites (glucose, lactate, pyruvate, alanine, free fatty acid, glycerol and ketone bodies) • Serum electrolytes, liver functions and acid - base status, C reactive protein • Ammonia • Amino acids • Total and free carnitine • Acylcarnitine profile • Insulin, C - peptide, growth hormone, IGF1, IGFBP3, cortisol and thyroid hormones • Galactosemia screen
Urine	<ul style="list-style-type: none"> • Ketones by dipstick • Organic acids and aminoacids • Reducing substances (galactose and fructose)
Others	<ul style="list-style-type: none"> • Ophthalmic examination • Cranial ultrasound scan and/ or MRI

Table 2. Suggested investigations in hypoglycemic patient with suspected metabolic/ endocrine disorder (Deshpande & Platt, 2005).

If neonate meets criteria for metabolic-hormonal disturbances, crucial point will be to obtain appropriate samples for examination of intermediary metabolites and hormones at the time of hypoglycemia. The second sample in a half an hour after episode may be useful to evaluate counter-regulatory response, mainly in newborns suspected of pituitary deficiency. If such samples are not obtained, the correct diagnosis may be delayed, furthermore, invasive testing and controlled fasting may be required. It can be helpful to prepare a hypoglycemia kit with suitable containers and instructions for instance of sudden hypoglycemic episode (Table 2). Further management should involve consultation with a specialist in pediatric endocrinology and metabolic medicine (Desphande & Platt, 2005).

2.1 Hormone deficiency

Some newborns with hypoglycemia are supposed to have pituitary deficiency, those suffering from midline defects (cleft lip or palate) and micropenis with undescended testes. At first, the basal sample of free thyroxine, TSH, cortisol, IGF-1, IGF BP-3, sex hormones should be recommended. Typically, lower concentrations of thyroxine, cortisol and IGF BP-3

are measured in infants with pituitary deficiency. Decreased IGF BP-3 level has greater value to diagnosis of growth hormone deficiency in infancy. Despite importance of evaluation IGF-1 levels in children, these are rarely helpful in neonates. In fact, serum IGF BP-3 should be performed as the test of choice in suspected neonatal growth hormone (GH) deficiency. The use of standard GH stimulation tests is not recommended in newborns, except for safe glucagon test 0,03–0,1 mg/kg. Cortisol and GH levels are measured in a basal sample, and furthermore in 5 consequent samples (0, 60, 90, 120, 150, 180 min). Cortisol and GH sampling half hour after clinically significant and laboratory proved low blood glucose level ($\leq 2,2$ mmol/l) can confirm GH deficiency, and protect child from prolonged redundant testing (Weintrob et al, 1998). Several mutation in genes involved in pituitary development (POUF1, PROP1, TPIT) has been reported in infants with hypoglycemia due to pituitary deficiency. Congenital hypopituitarism may not be diagnosed until a baby is several months old. Abnormal growth is usually noticed only after 1-2 years of life and recurrent hypoglycemia in infants with confirmed GH deficiency is an indication to start GH treatment, especially in those on thyroxine and hydrocortisone therapy (Randell et al, 2007).

Neonates with ambiguous genitalia are always suspected of congenital adrenal hyperplasia, although presenting clinical signs of mineral disturbances rather than hypoglycemia may be apparent from 2 to 4 weeks of life. Treatment with hydrocortisone and fludrocortisone should be started immediately in such infants, after appropriate hormonal sampling. Chromosome analysis, hormone measurements (especially 17-hydroxyprogesteron, androstendion, cortisol and testosterone) are necessary in diagnostic approach, the most common cause is 21-hydroxylase deficiency. If enzyme defect is confirmed by hormonal measurements, identification of mutation in genes (CYP 21, CYP 11 β , and other) should follow in management. Wolman disease and congenital adrenal hypoplasia, two other rare causes of adrenal failure have been described in neonates and infants (Randell et al, 2007).

2.2 Metabolic inborn error

Hypoglycemia induced by first feeding, especially in combination with vomiting, diarrhoea and jaundice, should be suspected from galactosemia (galactose-1-phosphate uridyl transferase deficiency or UDP galactose-4-epimerase deficiency). Exposure to milk results in acute deterioration of multiple organ systems, including liver dysfunction, poor feeding, weight loss, renal tubular dysfunction, neutropenia, coagulopathy and *Escherichia coli* sepsis. Galactosemia should also be excluded in all neonates with these findings and concomitant *E.coli* sepsis. Some screening programs in newborns have included galactosemia routinely. A galactose restricted diet will reverse effectively multiorgan dysfunction, and will eliminate the risk of hypoglycemia during childhood. However, long-term effect on mental functions, speech and ovarian function may persist despite appropriate dietary therapy in individuals with galactosemia (Leslie, 2003).

Nonspecific symptoms occurring 3-6 months after birth, such as failure to thrive and vomiting, may be a part of clinical picture of hereditary fructose intolerance due to fructose 1-phosphate aldolase deficiency. Exclusively breast-fed and formula-fed infants are healthy unless fruits and juices are added into diet. The worsening of symptoms and hypoglycemia with feeding should rise clinical suspicion. Low chronic exposure to fructose causes failure to thrive and chronic liver disease. Biochemical findings of elevated fructose level may be

confirmed by enzyme assay of liver or small intestinal biopsy. Treatment consists of strict dietary avoidance of fructose, sucrose and sorbitol (Wong, 2005).

Disorders of gluconeogenesis should be considered in infants with fasting hypoglycemia during intercurrent illness, especially in the case of positive family history to unexplained sibling death. Pattern of characteristically abnormal organic acids in urine is usually present in infants with disruption of gluconeogenesis. Fructose 1,6-diphosphatase is a key regulatory enzyme of gluconeogenesis from all substrates (fructose, glycerol, lactate and amino acids). Deficiency of such enzyme leads to hepatomegaly, hypoglycemic seizures and hyperventilation due to lactic acidosis and ketoacidosis. Developmental delay and mental retardation may be the consequence of untreated infants. Unlike hereditary fructose intolerance, liver and renal tubular dysfunction are atypical. Infants with fasting hypoglycemia and lactic acidosis should be suspected of defects of gluconeogenesis, diagnosis is confirmed by enzyme assay in liver biopsy. Chronic treatment consists of avoidance of fasting and reduction of fructose in diet, correction of metabolic acidosis is necessary (Langdon et al, 2008). Continuous nasogastric infusion may be helpful overnight and during intercurrent illness. Rarely, pyruvate carboxylase deficiency has been found. In addition to hypoglycemia, hyperalaninemia and lactic acidosis, elevated pyruvate is confirmed. Some infants develop hyperammonemia, hypercitrulinemia, hyperlysineemia and hyperprolinemia. Diagnosis may be proven by measurement of enzyme activity in fibroblasts. In addition to metabolic acidosis correction, substitution of Krebs cycle substrates has been suggested, as well as supplementation with coenzymes of pyruvate dehydrogenase complex - thiamine and lipoic acid (Ahmad et al, 1999). Except such genetic enzymatic defects, alcohol ingestion and salicylate treatment may cause iatrogenic block of gluconeogenesis.

Medium-chain acyl-coenzyme A dehydrogenase deficiency (MCAD) is the most frequent disorder of fatty acid oxidation. Neonatal screening in Pennsylvania has shown an incidence 1:9 000 live birth (Ziadeh et al, 1995). Although there is a significant heterogeneity in presentation of MCAD, the most common sign is intermittent hypoketotic hypoglycemia during intercurrent infection with decreased oral intake. Family history of sibling death rises suspicion. Severe form presents as a Reye-like syndrome with hyperammonemia, hepatocellular failure and coma. Affected patients could also be misdiagnosed with sudden infant death syndrome (Roe & Ding, 2001). Evaluation of suspected errors in fatty acid oxidation should first include the determination of plasma acylcarnitine profile by mass spectrometry and measurement of plasma total, esterified and free carnitine. Determination of urinary organic acids with assessment of dicarboxylic aciduria is also very useful. Patients, whose disorder cannot be confirmed by these tests, may require further evaluations, including assays of fatty acids oxidation and specific enzyme assays in cultured skin fibroblasts or lymphoblasts. Direct DNA mutational analysis can be performed, particularly in MCAD. Therapeutic approach consists of avoidance of fasting and high fat intake, although normal amounts of fats do not seem to be harmful. The use of cornstarch (1-2g/kg every 4 hours) and carnitine supplementation has been advocated (Rinaldo et al, 2002).

2.3 Neonates at risk of hypoglycemia

Prevention of low blood glucose concentrations is the goal of management in newborns at risk of hypoglycemia. In healthy appropriately grown term infants, facilitating normal feeding is all that is needed. Breast-fed neonates demonstrate lower blood glucose and

higher ketone concentrations than formula-fed ones. This starving, ketogenic response is typical for physiologic transition from fetal to neonatal metabolism, as in other mammals (de Rooy & Hawdon, 2002). For infants, who are able to tolerate enteral feeding, increasing amount of milk should be the first strategy. Although oral dextrose solution may be recommended, the milk contains approximately twice more energy as equivalent volume of 10% dextrose.

Severely IUGR neonates may be hypoglycemic in utero, delayed metabolic adaptation will be expected in those infants soon after birth. Cord blood glucose level determination may be helpful, the concentration less than 2,0 mmol/l can reveal IUGR infants at high risk of symptomatic hypoglycemia. In order to precede clinical consequences, appropriate intervention seems to be prophylactic intravenous glucose infusion as soon as possible (Desphande & Platt, 2005). In IUGR infants, early enteral feeding is recommended and breast-feeding is the approach of choice. If child remains hypoglycemic despite an adequate milk intake, intravenous glucose infusion at a rate equal to the hepatic glucose production 6-8 mg/kg/min (85-120 ml of 10% glucose/kg/24 hrs) is necessary. Due to functional hyperinsulinism in some IUGR infants, glucose intake may be increased (10 mg/kg/min or more) occasionally.

Preterm infants with respiratory distress (usually less than 32 weeks of gestation) require always intravenous glucose infusion, at least 6 mg glucose/kg/min. Near term infants are often able to suckle the breast or bottle but skillful support of nurse may be needed. Supplementation of milk with glucose polymers and energy supplements may increase the risk of necrotizing enterocolitis due to bowel osmolality (Desphande & Platt, 2005).

In infant of diabetic mother, the highest incidence of hypoglycemia occurs between 4-6 hr after birth, interval of onset may extend up to 48 hrs. Tighter metabolic control during pregnancy and delivery is associated with decreased frequency of neonatal hypoglycemia. In particular, maternal blood glucose more than 8 mmol/l during parturition is linked with higher risk of hypoglycemia in neonate. Insufficient metabolic compensation of pregnant diabetic woman is the reason of neonatal macrosomia due to prolonged fetal hyperinsulinism (Taylor et al, 2002). Management approach to neonate of diabetic mother consists of early enteral feeding and regular pre-fed glucose monitoring, unless the later blood glucose level is normal one. Excessive glucose infusion rate in baby is responsible only for another pancreatic stimulation and should be avoided. Similarly, administration of glucagon immediately after birth is not routinely recommended, otherwise rapid hepatic glucose release can further stimulate insulin secretion and augment the tendency to hypoglycemia.

The use of intravenous glucose bolus is inevitable in symptomatic infants with glycemia below the normal range. Recommended bolus therapy is 2 ml/kg of 10% glucose solution (200 mg glucose/kg). The dose has been efficacious in rapid release of clinical symptoms like as depressed alertness, hypotonia, apnoe or seizures, otherwise it usually restores normal blood glucose level without later hyperglycemia. Intravenous administration of bolus should be followed by an increase in the rate of glucose infusion. Treatment of neonatal hypoglycemia with intermittent boluses alone is not logical, the need for such boluses is an indication for rising continuous glucose infusion rate. Boluses of hypertonic (20% or 40%) glucose solutions should be avoided. In a similar way, gradual rather than large reduction in the rate of intravenous glucose infusion is helpful to maintain stable blood glucose concentration.

Glucagon promotes early neonatal glycogenolysis from liver and also stimulates gluconeogenesis and ketogenesis. Intravenous bolus dose of 200 µg/kg was used in previous studies, such administration may provoke further hypoglycemia due to hyperglycemia induced insulin secretion. Therefore, application of glucagon bolus should be followed by continuous glucose infusion. In a study of 55 neonates with hypoglycemia of various etiologies, continuous infusion of glucagon (0,5-1,0 mg/day) increased blood glucose concentration significantly within 4 hrs after starting of infusion. The frequency of subsequent hypoglycemia has been decreased with continuous glucagon therapy (Mirales et al, 2002). The occurrence of severe hyponatremia has been reported in a preterm infant, but the relationship with glucagon infusion seems to be unlikely (Charsha et al, 2003, Coulthard & Hey, 2002).

3. Management of neonatal hyperinsulinism

Most infants with hyperinsulinism present within neonatal period, although infantile and childhood forms are also described. In general, excessive glucose requirement with infusion rate more than 10 mg/kg/min is suspected of hyperinsulinism. Traditionally, the diagnosis of hyperinsulinism is based on demonstrating inappropriately high insulin concentration at the time of hypoketotic hypoglycemia (Table 3). Diagnosis is confirmed by insulin level more than 2,0 mIU/l and glycemia below 2,8 mmol/l at the same time. Intravenous administration of glucagon is followed by glycemic response bigger than 1,7 mmol/l within 15- 30 minutes in infants with hyperinsulinism (de Leon et al, 2008).

Criteria for diagnosing hyperinsulinism based on critical sample

Critical sample must be drawn at time of hypoglycemia (plasma glucose < 50mg/dl)

- Detecable insulin (>2 mIU/l)
- Low free fatty acids (< 1,5 mmol/l)
- Low ketones (plasma β hydroxybutyrate < 2,0 mmol/l)

Inappropriate glycemic response to 1mg intravenous glucogen at time of hypoglycemia (glucose rise > 30mg/dl in 20 minutes)

Table 3. Criteria for diagnosing hyperinsulinism based on critical sample (Langdon et al, 2008).

The majority of neonatal hyperinsulinism is transient, these form has been observed in neonates with maternal diabetes, Beckwith - Wiedemann syndrome, Sotos syndrome, Perlman syndrome, birth asphyxia, polycythemia, rhesus incompatibility and severe intrauterine growth retardation (Baujat et al, 2004). Such perinatal stress-induced hyperinsulinism may persist for several days to several weeks, but not longer than 6 months (Hoe et al, 2006). Infants with prolonged stress hyperinsulinism are usually good responders to diazoxide therapy. Glucocorticoids are not effective in controlling of hyperinsulinism.

Hyperinsulinism is the most common cause of persistent or recurrent hypoglycemia in infancy. Generally, the persistent hyperinsulinism is relatively rare (1:30 000- 1:50 000) but may lead to neurological damage and lifelong handicap. Up to 20% of infants suffering from congenital hyperinsulinism exhibits neurological defect (Menni et al, 2001). Approximately 60% of patients with persistent hyperinsulinism present within the first week of life, the

most severe forms start earliest. However, all of the genetic causes of hyperinsulinism may be initially diagnosed in older infants and children (Langdon et al, 2008).

Infants with congenital hyperinsulinism are usually born in term and macrosomic, similar as neonates of diabetic mothers. On the other hand, low birth weight or preterm birth does not exclude persistent hyperinsulinism (Aynsley-Green, 2000, Yap et al, 2004). Most infants are apparently macrosomic and plethoric and may have characteristic facial features with high forehead, large and bulbous nose, smooth philtrum and thin upper lip. Later in infancy, the only clinical sign may be unexplained developmental delay (de Lonlay et al, 2002 a).

Exomphalos in neonates with macrosomia and macroglossia enables to diagnose Beckwith-Wiedemann syndrome (BWS 1:10 000). Hyperinsulinemic hypoglycemia occurs approximately in 50% infants, and is usually mild and transient. Higher predisposition to childhood tumors has been described in BWS patients, analysis of chromosome 11p15 finding aberrant H19 and KCNQ1OT1 hypomethylation may identify patients at increased risk of cancerogenesis (Bliek et al, 2001). Sotos syndrome (cerebral gigantism) involves also combination of somatic overgrowth and hyperinsulinism, the major cause is haploinsufficiency of NSD1 gene (Baujat et al, 2004).

The appropriate management of hyperinsulinemic infants is based on maintaining of blood glucose above 3,5 mmol/l. Even though of sufficient enteral feeding, the supplemental 10-15% glucose intravenous infusion is often needed, otherwise glucose requirement is usually 15-20 mg/kg/min. A secure central intravenous access should be obtained immediately after diagnostic evaluation. If intravenous cannula is resited, intramuscular glucagon administration 100 µg/kg is recommended. Hyperinsulinemic infants require intensive medical care monitoring at a centre specialized in management of hyperinsulinism. Once the infant is stabilized, a planned transport should take place. Delayed referral to the centre may be the reason of neurologic consequences associated with disorder (Desphande & Platt, 2005).

The majority of transient forms of congenital hyperinsulinism will settle during the first month of life. This period can be spent evaluating of responsiveness to drugs therapies and attempting to introduce normal enteral feeding. After 4 weeks, as soon as diagnosis of congenital hyperinsulinism is confirmed, rapid genetic analysis of the affected child and parents using HPLC screening followed by sequencing of target genes should be recommended (Lindley & Dunne, 2005).

The most common and severe cause of persistent hyperinsulinism is due to loss of function mutation of the pancreatic β -cell K⁺ATP channel consisting of 2 subunits. K⁺ATP hyperinsulinism may be diffuse or focal. More than 100 mutations of ABCC8 (encoding SUR1 subunit) and 20 mutations of KCNJ11 (encoding Kir6.2 subunit) have been found so far. Neonates with recessive form present as a large for gestational age with very severe hypoglycemia immediately after birth, characteristic sign is usually poor responsiveness to diazoxide. Dominant form of K⁺ATP hyperinsulinism may occur in family members, the onset of milder hypoglycemic symptoms is often later in infancy and childhood. These patients reflect better responsiveness to diazoxide (Grimberg et al, 2001). In addition, defects in SUR1 subunit may be inherited in three different mechanism, loss of heterozygosity has been identified, except for recessive and dominant patterns. The association of recessive mutations with diffuse hyperinsulinism, as well as loss of heterozygosity with focal form, has been found in infants with SUR1 defects (Langdon et al, 2008).

The second most common form in infants is hyperinsulinism/hyperammonemia (HI/HA) syndrome caused by gain of function mutation of GLUD1 (encoding glutamate

dehydrogenase GDH). Most cases are sporadic due to de novo mutations. Approximately 20% of these disorders are familial with autosomal dominant inheritance. Typically, neonates suffering from HI/HA syndrome are appropriate for gestational age. Episodes of symptomatic hypoglycemia may not be recognized until 1-2 years of age. Patients with HI/HA syndrome have relatively mild fasting hypoglycemia. However, after ingestion of protein meal, severe protein-sensitive hypoglycemia can happen within 30-90 minutes. Diazoxide therapy is usually effective to control fasting and protein-induced hypoglycemia. Differential laboratory finding is slightly elevated ammonia level (60-150 $\mu\text{mol/l}$) without therapy requirement. The lack of clinical hyperammonemic symptoms may be explained by increased GDH enzyme activity in brain of affected individuals (Li et al, 2006). Less frequent form of congenital hyperinsulinism presenting with fasting hypoglycemia is due to activating mutations of GCK (glucokinase), sometimes showing autosomal dominant pattern. The age of onset and severity of symptoms varies markedly (Cuesta-Munoz et al, 2004). Rarely, mutation of HADHSC gene (encoding short chain L-3-hydroxyacyl-CoA dehydrogenase SCHAD) with autosomal recessive inheritance may be identified as a cause of hyperinsulinism in infants (Hussain et al, 2006).

Occasionally, congenital carbohydrate-deficient glycoprotein syndrome, also known as congenital disorders of glycosylation (CDG), has been identified as a cause of neonatal hyperinsulinism. Unlike other forms of hyperinsulinism, CDG often leads to involvement of other systems, especially the brain, liver, gut and skeleton. The diagnosis is usually confirmed by identification of hyposialylated serum transferrin by isoelectric focusing (Fang et al, 2004).

Less than 20% of neonates with persistent congenital hyperinsulinism will respond to diazoxide therapy, a K⁺ATP channel opener (De Lonlay et al, 2002 b). Diazoxide binds to the SUR1 subunit of the K⁺ATP channel. Infants with no functional K⁺ATP channels at the β -cell membrane are not expected to respond to diazoxide therapy. On the other hand, patients suffering from hyperinsulinism-hyperammonemia syndrome with normal K⁺ATP channel are more likely better responders than those with ABCC8 loss of function mutation. So genetic analysis of congenital hyperinsulinism is useful in predicting of drug responsiveness. The daily requirement of diazoxide varies between 5-25 mg/kg divided in several doses. Otherwise, diazoxide as a channel opener retains sodium and water, chlorothiazide has been successfully added to counteract this side event. Apart from acting as a diuretic, chlorothiazide has also direct β -cell potassium channel opening activity. In a purpose to supply sufficient glucose, large volumes of intravenous fluids are infused to hyperinsulinemic infants and enhance the danger of severe water retention (Silvani et al, 2004).

Somatostatin analogues are able to inhibit insulin secretion in various manners by inducing hyperpolarisation of β -cells, direct inhibition of the voltage-gated calcium channel and more distal insulin secretory pathways. Recommended dose of somatostatin analogues is 5-20 mg/kg/24 hrs intravenously or subcutaneously, usually in combination with diazoxide. If diazoxide is contraindicated and intravenous glucose requirement is too high, somatostatin therapy may be used as a first line treatment. Safety and efficacy of long term treatment in infants and children has been discussed (Dunne et al, 2004).

The intravenous administration of glucagon (1-10 $\mu\text{g/kg/hr}$) may be helpful in acute management of infants with hyperinsulinism, rising glycemia reflects the changes in gluconeogenesis and glycogenolysis. For long-term therapy, glucagon works like as insulin

secretagogue and is recommended usually in combination with other treatment lowering insulin secretion (Aynsley-Green, 2000). Considerable distinction has been reported on glycemic effect of Ca²⁺ channel blockers. According to reports of few centres, some hyperinsulinemic infants may profit from nifedipine chronic therapy (Lindley et al, 1996).

Selective drugs for hypoglycemic disorders

1. **Intravenous glucose rescue doses**
 - Dextrose emergency bolus: IV push 0,2g/kg bolus (2ml/kg of dextrose 10%), followed by D 10% continuous infusion of 5ml/kg/hr
 - If plasma glucose not corrected after 15 minutes, bolus 2ml/kg of 10% dextrose and increase continuous infusion by 25% to 50%
 2. **Glucagon (emergency treatment only in case of insulin-induced hypoglycemia)**
 - 1 mg intramuscularly or intravenously (0,03-0,1 mg/kg)
 - Side effects: vomiting and rebound hypoglycemia
 3. **Diazoxide (use in hyperinsulinism or sulfonyleurea overdose)**
 - 5 - 15mg/kg/day divided into two or three doses (if given by IV route, must be given over 15 minutes to avoid hypotension)
 - Start with maximum dose (15mg/kg to test), then lower as possible (responders usually require 10mg/kg or less)
 - Side effect: fluid and sodium retention, hypertrichosis
 4. **Octreotide**
 - Start at 2 to 5 mg/kg/day and increase to 20 mg/kg/day SC divided into 3 or 4 doses
 - Side effect: transient diarrhoea, abdominal discomfort, gallstones, transient growth impairment
 5. **Cornstarch (for glycogen storage disease)**
 - 1 - 2g/kg/dose (freshly prepare each dose by suspending in cold sugar - containing liquid)
 - Effect last 4 to 6 hrs
 - Not well absorbed in infancy
 - Side effect: diarrhoea
 6. **Carnitine (for free fatty oxidation disorder)**
 - 100mg/kg/day divided into three or four doses
 - Side effects: diarrhoea and fishy body odour
-

Table 4. Therapy of hypoglycemia (IV intravenous and SC subcutaneous) (Langdon et al, 2008)

Neonates with severe forms of congenital hyperinsulinism can usually be stabilised using the measures mentioned above (Table 4). After clinical improvement and stable glucose infusion rate, the oral feeding can start substantially. The response to enteral feedings, as well as protein load, may result in further stimulation of insulin secretion and recurrent hypoglycemia. In such infants, the appropriate management seems to be parenteral

nutrition, although this approach may also augment insulin release from β -cells (Magge et al, 2004).

Clinically, infants with focal lesions are indistinguishable from those with diffuse hyperinsulinism. The focal lesions are potentially curable by surgery, whereas the outcome of diffuse K+ATP hyperinsulinism is worse. Furthermore, near total pancreatectomy (95-98% of pancreas), invasive treatment of severe diffuse hyperinsulinism, is associated with a high risk of later development of diabetes mellitus. Focal lesions (usually less than 10 mm in diameter) are frequently not visible at laparotomy, the determination of appropriate diagnostic methods is necessary to differentiate focal hyperinsulinism from diffuse one. Significant different surgical approach depends on reliable and accurate diagnostic evaluation. Conventional imaging methods including ultrasound, octreotide scintigraphy, and magnetic resonance imaging are usually meaningless (Lindley & Dune, 2005).

Interventional radiology methods, such as transhepatic portal venous insulin sampling and selective pancreatic arterial calcium stimulation have only modest success and are technically difficult and highly invasive, predominantly in small infants. During sampling procedure, the blood glucose concentrations should be kept below 3,0 mmol/l to demonstrate insulin hypersecretion in all or in isolated samples. Such glycemia without ketones may provoke clinical signs, especially in hyperinsulinism. Recently, positron emission tomography (PET) scans with fluorine-18, L-3, 4-dihydroxyphenylalanine (18F-fluoro-L-DOPA) have been found to accurately discriminate focal form from diffuse hyperinsulinism. In infants with focal hyperinsulinism, there is a local accumulation of 18F-fluoro-L-DOPA. Combined PET and computed tomography (CT) images make lesion possible to be localized (Ericson et al, 1997).

4. Management of hypoglycemia in children and adults

Comparing to adults, children have very limited glucose homeostasis because of smaller reserves of liver glycogen and muscle protein. Moreover, glucose consumption is relatively high due to larger brain-to-body-mass ratio in children. For example, the fuel stores of a 10 kg infant are only 15% of those of an adult. The real consequence of mentioned differences is various approach to fasting in children and adults. Exposing infants to fasting is not without risk, particularly if fatty acid oxidation disorders or adrenal insufficiency are present (de Leone et al, 2008).

Infants younger than 1 year should not be fasted more than 24 hrs, while in older children the maximum fasting is 36 hrs. Adults usually require to decrease plasma glucose level below diagnostic threshold more than 48 hrs (maximally 72 hrs). The fasting test is interrupted, when the plasma glucose falls below 2,8 mmol/l. This starving may be ended sooner, if plasma β -hydroxybutyrate rises above 2,0 mmol/l or in the case of any clinical signs suggesting hypoglycemia. At the time of hypoglycemia, critical sampling of alternative fuels (ketones, lactate and free fatty acids), insulin and counter-regulatory hormones (mainly cortisol and growth hormone) is crucial (Table 5). The result of fasting test may be affected by β -blockers treatment and unrecognized hypothyroidism, these two possibilities should be excluded before fasting. Especially in suspicion of hyperinsulinism, the fasting test may be ended with intravenous glucagon administration to evaluate the glycemic response (de Leon et al, 2008).

	Fasting			
	Hypoglycemia			
	Acidosis		No Acidosis	
Fuel Response	Lactic acidosis	Ketoacidosis	Free fatty acids > 1,5 mmol/l	Free fatty acids < 1,5 mmol/l
Possible Disorders	G - 6 - Phosphatase deficiency Fructose 1,6 - diphosphatase deficiency Pyruvate carboxylase deficiency Normal neonates	Normal Ketotic hypoglycemic Glycogen storage disorder Growth hormone deficiency Cortisol deficiency	Fatty acid oxidation disorders Normal neonates	Hyperinsulinism Panhypopituitarism Small for gestational age, birth asphyxia
Further Test	Gluconeogenic precursors Glucagon stimulation test	Tests of pituitary & adrenal function Glucagon stimulation test	Acyl - carnitine profile	Glucagon stimulation test Tests of pituitary, adrenal, thyroid function Insulin assay Other tests for hyperinsulinism

Table 5. An algorithmic approach to hypoglycemia (de Leon et al, 2008).

4.1 Ketotic hypoglycemia

Ketotic hypoglycemia is the most common cause of low blood glucose level in childhood. Usually, ketotic hypoglycemia begins as recurrent morning episodes of fasting hypoglycemia at the age of 2 or 3. The most of cases disappear spontaneously at the age of 8 to 9. Typically, partial or complete vomiting of evening meal is reported by parents in history. Especially, hypoglycemic episodes are likely to occur during periods of intercurrent illness with limited food intake. At the time of documented hypoglycemia, high level of ketones are measured in blood and urine, the plasma insulin concentration is typically low (< 2 mIU/l). Plasma alanine values are markedly reduced in children with ketotic hypoglycemia after overnight fasting. Infusions of alanine produce a rapid rise in plasma glucose concentration without significant changes in lactate or pyruvate levels. This suggests that a deficiency of substrate, rather than defect in gluconeogenesis, plays a role in etiopathogenesis. Alanine, as a major gluconeogenic amino acid precursor, is released from muscle during periods of caloric reduction. Children suffering from ketotic hypoglycemia are usually smaller than those of same age, reduced muscle mass in such patients may partially explain decreased supplies of gluconeogenic substrates (Stanley, 2006).

The diagnosis of ketotic hypoglycemia can be claimed only after exclusion of the others. Recurrent hypoglycemia with ketosis may occur in the case of hormone deficiencies, defects

in gluconeogenesis and glycogen metabolism. Sometimes, the diagnosis demands the confirmation gained by supervised fasting. Low blood glucose level in combination with elevated ketones and free fatty acids develops within 14 to 24 hrs in most children with ketotic hypoglycemia. Prevention of ketotic hypoglycemia involves frequent high-carbohydrate feedings, as well as overnight fasting should be shortened. The child with ketotic hypoglycemia should not fast more than 12 hrs. During intercurrent illness, parents ought to test the urine of child, the presence of ketones precedes hypoglycemia by several hours, and such ketones in urine may be the indicator of subsequent low blood glucose. In the presence of ketonuria, high-carbohydrate liquids should be offered to child. Vomiting child with ketotic hypoglycemia should be referred to the hospital for intravenous glucose administration (Langdon et al, 2008).

4.2 Hyperinsulinism

All genetic causes of hyperinsulinism may be diagnosed later in childhood, these are usually not so severe as persistent neonatal forms. In adolescence and adulthood, insulinoma appears more frequent cause of hyperinsulinism comparing to genetic ones. Insulin-secreting adenomas (insulinoma) of pancreas are extremely rare in young children, at this age diffuse or focal hyperinsulinism is more common. Insulinomas may occur sporadically, but familial form as a part of MEN 1 should be considered. Exclusion of parathyroid, pituitary and pancreatic hormone overproduction should be done in insulinoma patient and in family. MEN 1 may be confirmed by analysis of mutations of gene, encoding menin (Greenberg et al, 2000). Routine imaging of the pancreas (abdominal ultrasound, CT, MRI) often fails to reveal the tumor, unless it is bigger than 2 cm. Insulinomas are usually invisible on octreotide scan. Elaborating noninvasive diagnostic methods, the endoscopic ultrasonography seems to be the most helpful before surgery, higher sensitivity (90%) is described only in intraoperative ultrasonographic investigation. In adolescents and adults, invasive pancreatic arterial stimulation with calcium and subsequent venous sampling of insulin levels may localize the insulinoma to a region of pancreas, method is technically difficult in small children. Accurate diagnosis of hyperinsulinism must precede all invasive examinations and surgery (Hirshberg et al, 2000). Factitious hyperinsulinism ought to be strictly excluded, especially in puberty and adolescence. In spite of true hyperinsulinism, C-peptide level is low in the case of intoxication with human insulin. However, both true hyperinsulinism and sulfonyleurea poisoning show high C-peptide concentration. If iatrogenic hyperinsulinism is suspected, the concentration of sulfonyleurea drugs should be measured by specific toxicologic examination (Marks & Teale, 1999). Small number of children and adults may suffer from hypoglycemic seizures or syncope due to hyperinsulinism occurring with anaerobic exercise. The condition is inherited in an autosomal dominant pattern (Meissner et al, 2001).

4.3 Counter-regulatory hormone deficiency

Four hormones are involved in maintaining blood glucose level, but only cortisol and growth hormone deficiency are usually examined as a cause of hypoglycemia. Although all forms of hypocorticism may present by hypoglycemia, ACTH deficiency or unresponsiveness is more likely reflected in clinical sign of hypoglycemia than primary adrenal failure. Iatrogenic suppression of adrenal function is one of the most common causes of ACTH deficiency, but may be underdiagnosed due to absence of typical electrolyte

abnormalities. Vomiting, hypotension and hypoglycemia can be provoked by a stressful event in a child who weaned high-dose glucocorticoid therapy. Milder clinical manifestation may be caused by topical, inhaled or intranasal glucocorticoid preparations. Such treatment is advocated for many persons, and combination of these forms may lead to episodic hypoglycemia and can have possible impact to growth in childhood (Pinney et al, 2007). ACTH deficiency should be excluded in obese patient with red hair, especially before planned surgery. POMC mutations has been indentified as a cause of hypocorticism in this atypical clinical presentation (Krude et al, 1998). Idiopathic ACTH deficiency can be acquired in childhood, adolescence and also later in life. An association with autoimmune thyroiditis or celiac disease suggests autoimmune hypophysitis. Detailed history and examination are recommended to exclude pituitary damage, e.g. head trauma, pituitary infarction, infection, cranial radiation and tumors.

Patients with primary adrenal insufficiency are hyperpigmented due to oversecretion of proopiomelanocortin (POMC) and subsequently high ACTH and MSH levels, hypoglycemia is usually associated with typical mineral disturbances. In adolescence and adulthood, the common cause is autoimmune adrenalitis. Other autoimmune disorders should be considered (as a part of APS1 or APS2a), the positivity of organ-specific antibodies (ACA, anti-21-hydroxylase) is helpful in diagnostic approach. Typically, hypoparathyroidism and mucocutaneous candidosis precede adrenal failure in child with autoimmune polyglandular syndrome type 1 (APS1), defect in autoimmune regulator gene (AIRE) has been determined with recessive inheritance. In boys with proven adrenal failure, adrenoleukodystrophy should be excluded. This X-linked recessive disorder is detected by high levels of very long-chain fatty acids in urine. Milder form - adrenomyelopathy develops in childhood and adolescence, and neurological disease follows 10-15 years later. Severe form is much rare and starts in infancy. Hyperpigmentation and high ACTH level are also found in ACTH resistance (Allgrove syndrome - tripple A), inherited autosomal dominantly. Main features are achalasia, alacrimia and adrenal failure, patients suffer from autonomic dysfunction and progressive neurological symptoms. Mutation in ALADIN gene has been found in patients with tripple A syndrome (Randell et al, 2007).

GH deficiency may be either isolated, or as a part of panhypopituitarism. Two stimulation tests (GH<10 ng/ml) are required for diagnosis in children with growth retardation (SDS<-2), hypothyroidism and celiac disease should be excluded before testing. One test may be sufficient in the case of positive history to cranial radiation, or MRI imaging of empty sella, septooptic dysplasia or corpus callosum agenesis. After head surgery due to craniopharyngeoma, observing period without GH therapy is 2 years at least. In the case of complete pituitary insufficiency, the significant growth rate slowing, low IGF1 level and previously claimed three hormone deficiencies, any testing is not necessary. Moreover, provocation of hypoglycemia may be harmful and dangerous due to lack of two counter-regulatory hormones in panhypopituitaric child. Imaging findings, such as agenesis of corpus callosum, septooptic dysplasia or empty sella must increase clinical suspicion (Rosenfeld & Cohen, 2008).

Thirty minutes after hypoglycemia, sampling of hormones may reveal counter-regulatory deficiency more sensitively than measurement of critical sample. At the time of low blood glucose level, higher concentrations of cortisol (>500 nmol/l) and GH (>10 ng/ml) exclude substantial lack of these hormones. However, decreased counter-regulatory hormones in critical sample are not diagnostic for hormonal deficiencies. The peak of these hormones is

present approximately 30 minutes after hypoglycemic episode confirmed by laboratory blood glucose measurement below diagnostic threshold (<2,8 mmol/l). Such information about duration of hypoglycemia can not be usually obtained at the time of critical sampling. On the other hand, measurement of insulin and C-peptide levels at the time of low blood glucose level remains crucial for diagnosis of hyperinsulinism.

Teoretically, epinephrine deficiency may contribute to hypoglycemia of adrenal failure. However, hypoglycemia is rare in patients with bilateral adrenalectomy on adequate glucocorticoid replacement. Similarly, diabetic patients exhibit diminished epinephrine secretion more probably due to repeated hypoglycemia. Reduction of insulin-induced hypoglycemia can usually restore normal catecholamine response. Impaired glucagon secretion also increases the risk of hypoglycemia in patients with type 1 diabetes (Langdon et al, 2008).

4.4 Glycogen storage disease

Glucose is stored as a glycogen in the liver, muscles, and kidneys. If there is defect in formation or breakdown of glycogen, hypoglycemia may take part. In such group of metabolic inborn errors, glycogen storage disease (GSD) type 1 (glucose-6-phosphatase deficiency) is the most common cause of hypoglycemia. Appart from defect in glycogen metabolism, glucose-6-phosphatase deficiency is also essential enzyme for gluconeogenesis. Disruption of two metabolic pathways in GSD type 1 leads to significant persistent or recurrent hypoglycemia. Fortunately, glucose values within the range 30-50 mg/dl (1,7-2,8 mmol/l) are usually well tolerated, reflecting the adaptation of the brain to alternative fuel sources (lactate). Despite subtle clinical picture at the time of marked hypoglycemia, counter-regulatory hormones are elevated appropriately. Consequent promotion of glycogenolysis, gluconeogenesis and lipolysis increases lactate, triglycerides and ketones level. Clinically, glucose-6-phosphatase deficiency leads to massive glycogen stores and progressive hepatomegaly, renal tubular disease and malabsorbtion, later growth retardation is common. In addition to recurrent hypoglycemia, there is also lactic acidosis, elevated lipid levels and hyperuricemia in children with GSD type 1. Most cases are diagnosed in childhood, although sometimes GSD presents as a neonatal hypoglycemia. Diagnosis is made by enzymatic studies of liver, kidney or intestine biopsy tissue or by elaborating specific gene mutations. Availability of mutation analysis has made the need for liver biopsy obsolete. Management approach involves continuous nasogastric or gastrostomy nocturnal feeding (6-8 mg/kg/min of glucose) and cornstarch supplementation (1-2g/kg every 4 hrs). Patients are fed every 2 hrs during the day, and glucose should be continuously provided overnight.

GSD type 3 (amylo-1,6-glucosidase deficiency) exhibits similar laboratory and clinical findings, such as hepatomegaly and growth failure, occasionally progressive muscle weakness and cardiomyopathy has been recorded. GSD type 6 and 9 (liver phosphorylase deficiency) has a comparatively benign course, mild episodes of hypoglycemia are not usually associated with lactic acidemia and hyperuricemia. Furthermore, elevated transaminase and hyperlipidemia are measured, affected children are investigated for hepatomegaly, hypotonia and muscle weakness. Most of these clinical features resolve by puberty, although some individuals may have a problem with cardiomyopathy, myopathy and renal tubular acidosis. In patient with concomitant liver and muscle involvement, the use of low-carbohydrate high-protein diet has been suggested to protect muscle from lack of

alanin. Biochemical studies of leucocytes may confirm the diagnosis of GSD, except type 1 and 0. Glycogen synthase deficiency (GSD 0) is a rare but probably under-diagnosed cause of hypoglycemia. Fasting hypoglycemia is ketotic and unlike of other GSD, hepatomegaly is not observed. Diagnosis of GSD 0 can be determined by liver biopsy, recently mutation analysis of glycogen synthase gene has been available (Weinstein et al, 2006).

Glycogen accumulation in liver and kidney may be caused by GLUT2 deficiency (also known as Fanconi-Bickel syndrome). GLUT2 allows glucose transport across cell membrane of β -cells, renal tubule cells and hepatocytes. Except postprandial hyperglycemia due to reduced glucose transport on β -cell, clinical and laboratory findings are similar to Gierke disease (GSD type 1). Children suffer from fasting hypoglycemia, postprandial hyperglycemia, glucosuria, phosphaturia, aminoaciduria and metabolic acidosis. Furthermore, hepatomegaly, hypophosphatemic rickets and severe growth retardation can be present (Santer et al, 2002). Unlike GLUT2 deficiency, GLUT1 is responsible for glucose transport across blood-brain barrier. The clinical consequence varies from classic picture of developmental encephalopathy with seizures to atypical presentations, e.g. mental retardation, intermittent ataxia, choreoathetosis, dystonia and dysarthric speech. The diagnosis is confirmed by hypoglycorrachia in cerebrospinal fluid despite normal plasma glucose concentration. Recent discovery of this condition may explain previously longtime reported positive effect of ketogenic diet in some patients with neurologic defect. The ketogenic diet successfully controls the seizures in patients with GLUT1 deficiency, but has smaller effect on the cognitive function (Wang et al, 2005).

4.5 Autoimmune hypoglycemia

Autoimmune hypoglycemia can result from antibodies directed either against insulin or insulin receptor, and may occur in all ages. The hypoglycemia is most often postprandial, but may be fasting. Laboratory findings are usually similar to exogenous hyperinsulinism (high insulin and low C-peptide) in patients with anti-insulin antibodies positivity, whereas autoimmune hypoglycemia due to anti-insulin receptor antibodies shows typically undetectable insulin and C-peptide level. Rarely, antibodies directed against surface antigens on β -cells has been reported as a cause of autoimmune hypoglycemia (Redmon & Nutal, 1999).

4.6 Reactive hypoglycemia

The term of idiopathic postprandial syndrome, also known as reactive hypoglycemia, has been used for any clinical symptoms suggesting hypoglycemia that occur 2-4 hours after meal. Many healthy children and adults may have glycemia less than 60 mg/dl (3,3 mmol/l) without clinical presentation postprandially, consequently the oral glucose tolerance test has as a little diagnostic value in this syndrome. Most patients are adolescent girls with positive family history of similar symptoms in mother. At first, diagnosis such as panic attack, hyperventilation, vasovagal syncope and orthostatic hypotension should be excluded. Diagnosis of reactive hypoglycemia requires confirmation of low blood glucose level at the time of clinical symptoms suggesting hypoglycemia, and exclusion of other pathologic conditions (e.g. hyperinsulinism).

4.7 Alimentary hypoglycemia

All patients with Nissen fundoplication and gastrostomy tube are at risk of alimentary hypoglycemia. After surgery, rapid absorption of high-glucose fluids causes

hyperinsulinism, responsible for hypoglycemia in 1-2 hours later. This condition, known as a late (glucose) dumping may occur in one third of patients with fundoplication and gastric tube. In long-term management, an avoidance high load of rapid carbohydrates, a supplementation of acarbose of 12-75 mg per dose, and a complex carbohydrate formula may be successful (Ng et al, 2002).

4.8 Hypoglycemia induced by exogenous agents

Many medicaments may cause hypoglycemia as a side effect, directly or indirectly. Unlike to direct effect of β -blockers, discontinuation of chronic high-dose inhaled corticosteroid treatment and subsequent adrenal suppression might cause hypoglycemia indirectly. The correct attitude to any person presenting with hypoglycemia is awareness of detailed drug history concerning all family members. Common causes of low blood glucose level due to poisoning are paracetamol or salicylate overdoses, sulfonyleurea ingestion and insulin administration. Especially, insulin overdoses should be considered, if insulin concentration is too high despite of suppressed C-peptide level. In such patients, family history is usually positive for type 1 diabetes treated by human insulins. Administration of insulin analogues may not be detected by immunoassay, the serum insulin concentration may be falsely low. Recommended treatment is glucose ingestion or infusion, in case of insufficiency of these procedures, the successful use of diazoxide and octreotid has been reported (Lheurex et al, 2005). Sometimes, antidotes are necessary, for example, paracetamol poisoning requires addition of N-acetylcysteine. Similarly, salicylate intoxication may initiate changes in glucose metabolism, hyper- and hypoglycemia have been reported. Alcohol consumption reduces gluconeogenesis, hypoglycemia may occur in a several hours after acute intoxication. Ingestion of plants such as cocklebur (*Xanthium stumarium*) can cause hypoglycemia, kidney or liver dysfunction, and large amount may lead to multi-organ failure (Randell, 2007).

4.9 Hypoglycemia in non-insulin secreting tumors

Hypoglycemia has been reported in patients with non-insulin secreting tumors, predominantly large retroperitoneal ones. The serum evaluation of such patients shows elevated insulin-like growth factor 2 (IGF2). IGF-2 activates IGF-1 receptor and cross activates insulin receptor, causing hypoglycemia. In management approach, the method of choice is surgical removal of tumor. Some authors refers to success with growth hormone treatment up to the time of definitive surgery (Agus et al, 1995). However, this approach may be contradictory and needs other evidence.

4.10 Hypoglycemia in critical illness and organ failure

Approximately 30% of patients with severe malaria suffer from hypoglycemia, and the presence of low blood glucose seems to be associated with increased mortality in malaric patients. In addition, the therapy for malaria can contribute to hypoglycemia, in particular, quinine stimulates insulin secretion. Hypoglycemia is also common in other critically ill patients and has been reported in organ failure or severe disease, such as sepsis, head injury, heart failure, chronic renal failure, acute hepatic necrosis, pancreatitis, severe enteritis and multiple organ failure. Etiopathogenesis of hypoglycemia in these patients is often multifactorial: lack of substrate, undernutrition, accelerated glucose consumption, impaired gluconeogenesis, misplaced infusion line, cytokine and drug effect (Langdon et al, 2008). On

the other hand, an acute illness may reveal latent disorder of glucose metabolism (Weinstein et al, 2001).

4.11 Hypoglycemia in diabetes mellitus

In diabetic patients, clinical symptoms suggesting hypoglycemia should be promptly treated by rapid carbohydrate intake, 15 g of carbohydrates are recommended to 50 kg patient as usual. If signs last in 15 minutes, the same dose of carbohydrates should be taken. Clinical presentation of severe hypoglycemia, such as seizures and unconsciousness, must be cured by intramuscular or subcutaneous administration of glucagon with assistance of another person. The incidence of hypoglycemia induced by insulin therapy is higher than those caused by sulfonylureas. However, pre-existing renal failure may increase the risk of hypoglycemia in patients on sulfonylurea therapy. Measurements of a particularly low HbA1c level should be suspected of unknown hypoglycemic episodes in past.

The frequency of severe hypoglycemia is declining due to improvement of techniques, therapeutic strategies and insulin structure (Baunduceau et al, 2010). Hypoglycemia may be harmful in patients with history of ischemic heart disease, association between severe hypoglycemia and sudden death has been described. Prolonged duration of type 1 diabetes is linked to higher risk of severe hypoglycemia due to profound lack of insulin, furthermore, protective hormone response may be diminished (Heller, 2010). In ADVANCE study, an increase in the frequency of severe hypoglycemia was found in elderly diabetics presenting with substantial cognitive disorders. However, dementia alone is a significant risk factor for occurrence of severe hypoglycemic episodes due to mistakes in diabetes management (Bauduceau, 2010). Similarly, infants and small children are not able to manage own diabetes, hypoglycemia must be resolved by help of another person, so all hypoglycemia in such patients should be considered as a serious.

During exercise, diabetic patients are usually at risk of glucose declining, sometimes falling to hypoglycemic levels. Adequate carbohydrate replacement during and after exercise seems to be the most important measure to prevent hypoglycemia, an insulin reduction from 20 to 30% can be reasonable only for exercise lasting more than one hour (Grimm et al, 2004). Repeated unexpected low blood glucose levels in type 1 diabetes (DM 1) may be the indicator of associated disorders. All patients with DM 1 requiring significant reduction of insulin dose, should be testing for autoimmune hypothyroidism, hypocorticism and celiac disease.

5. Conclusion

Diagnostic approach to hypoglycemia should be based on critical sample of intermediate metabolites and hormones at the time of laboratory proven low blood glucose level as well as 30 minutes after hypoglycemic episode. Authors suggest that repeating second sampling may be more helpful for determination of deficiency of counter-regulatory hormones. All management effort should be done to obtain such measurement as soon as possible, with consequent quick and appropriate treatment. Delayed or incorrect diagnosis of hypoglycemic symptoms may lead to many different irreversible neurologic disturbances, especially in infants and small children.

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Over the last few decades the prevalence of diabetes has dramatically grown in most regions of the world. In 2010, 285 million people were diagnosed with diabetes and it is estimated that the number will increase to 438 million in 2030. Hypoglycemia is a disorder where the glucose serum concentration is usually low. The organism usually keeps the serum glucose concentration in a range of 70 to 110 mL/dL of blood. In hypoglycemia the glucose concentration normally remains lower than 50 mL/dL of blood. Hopefully, this book will be of help to many scientists, doctors, pharmacists, chemicals, and other experts in a variety of disciplines, both academic and industrial. In addition to supporting researcher and development, this book should be suitable for teaching.

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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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