Indian J Pediatr (January 2014) 81(1):58–65
DOI 10.1007/s12098-013-1135-3

SYMPOSIUM ON PEDIATRIC ENDOCRINOLOGY

Neonatal Hypoglycemia

Ved Bhushan Arya · Senthil Senniappan · Maria Guemes · Khalid Hussain

Received: 4 April 2013 / Accepted: 10 June 2013 / Published online: 1 August 2013

Abstract Glucose is essential for cerebral metabolism. Unsurprisingly therefore, hypoglycemia may result in encephalopathy. Knowledge of the homeostatic mechanisms that maintain blood glucose concentrations within a tight range is the key for diagnosis and appropriate management of hypoglycemia. Neonatal hypoglycemia can be transient and is commonly observed in at-risk infants. A wide range of rare endocrine and metabolic disorders can present with neonatal hypoglycemia, of which congenital hyperinsulinism is responsible for the most severe form of hypoglycemia. Collection of appropriate blood samples for hormones and intermediary metabolites during an episode of hypoglycemia is critical for diagnosis and appropriate management. Prompt diagnosis with aggressive early intervention remains the mainstay of treatment to avert irreversible brain damage.

Keywords Neonatal hypoglycemia · Congenital hyperinsulinism · Glycogen storage disorders

Introduction

Glucose is an essential fuel for brain metabolism. Consequently, low blood glucose levels may result in brain injury. There has not been a consensus among the experts in the field on the cut-off value to define neonatal hypoglycemia [1]. Operational thresholds for management have been identified. For any baby with signs and symptoms consistent with hypoglycemia, blood glucose should be maintained above 45 mg/dL (2.6 mmol/l) unless there is a suspicion of hyperinsulinism when a higher threshold (65 mg/dL or 3.5 mmol/l) should be used [2].

Knowledge of the homeostatic mechanisms that maintain blood glucose concentration between the relatively narrow ranges of 65–100 mg/dL during fasting is the key for the diagnosis and appropriate management of hypoglycemia.

During feeding, absorbed glucose in excess of immediate requirements is stored as glycogen in the liver to be utilized during fasting. Between feeds, normal blood glucose levels are maintained by glycogenolysis (liver) and gluconeogenesis (liver and kidney). Gluconeogenesis is a process by which glucose is produced from non-carbohydrate carbon substrates such as pyruvate, lactate, glucogenic amino acids (especially alanine) and glycerol.

The human fetus receives continuous supply of nutrients through placental circulation. After birth, the newborn infant's metabolism must adapt to the fast-feed cycle. The hormonal changes (decrease in plasma insulin and increase in glucagon and catecholamines) at birth allow the newborn infant to adapt successfully to interrupted supply of nutrients.

Disturbances in this smooth transition can result in neonatal hypoglycemia. Most cases of neonatal hypoglycemia are due to delay of the normal processes of metabolic adaptation after birth and occur in at-risk infants (transient hypoglycemia; Table 1). An underlying metabolic or hormonal etiology should be suspected when the hypoglycemia is of unusual severity or occurs in an otherwise low-risk infant. Some metabolic and hormonal conditions presenting with hypoglycemia in the neonatal period are shown in Table 2.

V. B. Arya · S. Senniappan
Clinical and Molecular Genetics Unit, University College London Institute of Child Health, London Centre for Pediatric Endocrinology, Great Ormond Street Hospital for Children, London, UK

M. Guemes
London Centre for Pediatric Endocrinology, Great Ormond Street Hospital for Children, London, UK

K. Hussain (✉)
Developmental Endocrinology Research Group, Clinical and Molecular Genetics Unit, University College London Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK
e-mail: khalid.hussain@ucl.ac.uk

Table 1 Infants at-risk of hypoglycemia

Maternal conditions	Pre-gestational or gestational diabetes
	Medication (β-blockers, oral hypoglycemic agents, intrapartum glucose administration)
Neonatal conditions	Prematurity
	Small for gestational age/ IUGR
	Large for gestational age
	Perinatal hypoxia-ischemia
	Infection
	Polycythemia
	Hypothermia
	Parenteral nutrition
	Syndromic features, midline defects

Transient Neonatal Hypoglycemia

In this group, the hypoglycemia occurs in at-risk infants and resolves spontaneously within a few days after birth (Table 1). The cause of hypoglycemia in intrauterine growth restricted (IUGR) infants is multifactorial including depletion of liver glycogen, decreased fat and protein reserves, decreased fat oxidation, low gluconeogenic rate and increased glucose demand as a result of perinatal hypoxia and a relatively large brain mass [3]. Maternal diabetes with poor glycemic control leads to chronic hyperglycemia in utero and is a common cause of transient neonatal hyperinsulinemic hypoglycemia (HH). Glucose crosses the placenta by facilitated diffusion, thereby imposing upon the fetus a carbohydrate surplus. The fetus responds with increased secretion of insulin, which stimulates protein, lipid and glycogen synthesis and causes macrosomia.

Perinatal stress is an important cause of hypoglycemia, the etiology of which has been well-defined in experimental animal fetuses [4]. The stress response to hypoxia leads to intense glycogenolysis to provide glucose substrate, which leads to depletion of glycogen reserves. There may also be excessive release of insulin due to asphyxial damage to the pancreatic β-cells. Occasionally, some patients with IUGR and perinatal asphyxia have a protracted form of hypoglycemia which resolves over several months and may require treatment with diazoxide [5]. Sepsis with associated increased metabolic rate and toxic effects on hepatic metabolism could lead to neonatal

Table 2 Metabolic and endocrine causes of neonatal hypoglycemia

Hyperinsulinism	Transient
	Infant of diabetic mother
	Perinatal asphyxia
	Rhesus hemolytic disease
	Intrauterine growth restriction (IUGR)
	Beckwith-Wiedemann syndrome
	Congenital
	ABCC8/ KCNJ11/ GCK/ GDH/ HADH/ HNF4A
Hypoinsulinemic hypoglycemia	Activating *AKT2* mutations
Counter-regulatory hormone deficiency	Growth hormone deficiency
	Adrenal insufficiency
Fatty acid oxidation disorders	Medium chain acyl-CoA dehydrogenase deficiency
	Long chain acyl-CoA dehydrogenase deficiency
	Short chain acyl-CoA dehydrogenase deficiency
Defects in ketone body synthesis/ utilization	HMG CoA synthase deficiency
	HMG CoA lyase deficiency
Carnitine deficiency (primary and secondary)	Carnitine palmitoyl transferase deficiency (CPT 1 and 2), Carnitine deficiency
Gluconeogenic disorders	Fructose-1, 6-bisphosphatase deficiency, Phosphoenolpyruvate carboxykinase (PEPCK) deficiency, Pyruvate carboxylase deficiency
Glycogen storage disorders	Glucose-6-phosphatase deficiency
	Amylo 1–6 glucosidase deficiency
	Glycogen synthase deficiency
Defects in glucose transport	GLUT 1/2/3 transporters defects
Other metabolic conditions	Galactosemia, Fructosemia, Tyrosinemia, Glutaric aciduria type 2, Maple syrup urine disease
	Propionic acidemia

hypoglycemia. The decrease of hepatic glycogen stores together with impaired nutrition and malabsorption could lead to hypoglycemia in neonates in congenital heart disease.

Persistent Neonatal Hypoglycemia

Congenital Hyperinsulinism

The most common cause of recurrent and persistent hypoglycemia in the newborn period is congenital hyperinsulinism (CHI). CHI is characterized by inappropriate and unregulated insulin secretion from pancreatic β-cells in the presence of a low blood glucose concentration [6]. The early recognition, diagnosis and immediate management is important, as delay in the diagnosis and management can lead to hypoglycemic brain injury [7]. CHI is a heterogeneous condition in terms of clinical presentation, histology and molecular genetics [8].

Glucose homeostasis is maintained by the pancreatic β-cells by linking insulin secretion to glucose metabolism (Fig. 1) [9]. Glucose metabolism raises the intracytosolic ATP/ADP ratio, which inhibits the plasma membrane sulfonylurea receptor 1(SUR 1) subunit of ATP sensitive potassium channel (K_{ATP} channel). This result in the closure of the K_{ATP} channel, cell membrane depolarization and subsequently, Ca2+ influx into the cell *via* voltage gated calcium channels. The increase in the intracellular concentration of calcium triggers the release of insulin. When glucose levels are low, K_{ATP} channels are open and potassium diffusing *via* these channels maintains the resting membrane potential at a hyperpolarized level. However in CHI, the synchronized activity between glucose metabolism and insulin secretion is altered leading to inappropriate secretion of insulin during hypoglycemia.

CHI is caused by mutations in the key genes that are involved in regulation of insulin secretion from the pancreatic β-cells. So far, mutations in *ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, HNF4A, UCP2* and *HNF1A* have been identified to be involved in the pathogenesis of CHI [10, 11]. The most common causes of diffuse CHI are mutations in the genes *ABCC8* and *KCNJ11*. These two genes encode for the SUR1 (sulphonylurea receptor 1 subunit) and Kir6.2 (inward-rectifying potassium channel pore-forming subunit) proteins respectively which constitute the K_{ATP} channel of the pancreatic β-cell membrane [10].

The recessive inactivating mutations in *ABCC8* and *KCNJ11* usually cause severe CHI, which is unresponsive to medical treatment with diazoxide. Dominant inactivating mutations in *ABCC8* and *KCNJ11* usually cause CHI with a milder phenotype [12].

There are two histological subtypes of CHI: diffuse and focal [13]. The whole of the pancreas is affected in the diffuse form, whilst only a portion of the pancreas is involved in the focal from. The diffuse form is inherited in an autosomal recessive (or dominant) manner whereas the focal form is sporadic in inheritance. The focal lesions are localized by using a specialized positron emission tomography scan using Fluroine-18L-3, 4-dihydroxyphenyalanine isotope (^{18}F-DOPA-PET) [14]. The diffuse forms of CHI that do not respond to medical therapy need near total pancreatectomy (with the risk of diabetes mellitus and pancreatic exocrine insufficiency) whereas the focal forms are cured by focal lesionectomy [8].

Hyperinsulinism-hyperammonemia syndrome (HI/HA), the second most common form of CHI is associated with activating missense mutations in the *GLUD1* gene, which encodes the mitochondrial matrix enzyme, glutamate dehydrogenase (GDH). Patients present with recurrent symptomatic postprandial hypoglycemia following protein-rich meals (leucine-sensitive hypoglycemia) as well as fasting hypoglycemia accompanied by asymptomatic elevations of plasma

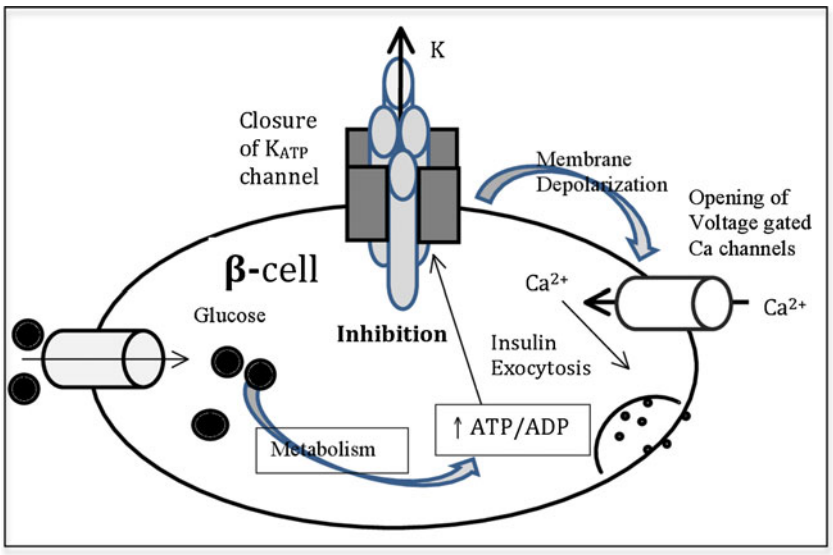

Fig. 1 Schematic diagram of pancreatic β-cell showing glucose metabolism controlling insulin release

ammonia [15]. Patients with HI/HA syndrome have more neurological complications such as epilepsy and learning disabilities [16]. Routine measurement of plasma ammonia concentrations in all patients with hypoglycemia is an essential screening test for the disorder.

Mutations in the *HNF4A, HNF1A* and *GCK* genes cause maturity-onset diabetes of the young (MODY) as well as CHI [11, 17]. The severity of CHI in these patients varies from diet-controlled neonatal hypoglycemia to persistent HH requiring diazoxide treatment and even surgery in some patients with *GCK* mutation [18].

Hyperinsulinemic hypoglycemia can also be associated with developmental syndromes like Beckwith-Wiedemann syndrome or rare metabolic conditions like congenital disorders of glycosylation [19, 20].

Patients with CHI are at increased risk of neurological damage due to hypoglycemia as insulin drives glucose into skeletal muscle and adipose tissue and also inhibits glucose production by glycolysis and gluconeogenesis [2]. In addition, insulin inhibits fatty acid release and ketone body synthesis thereby depriving brain from both glucose and ketone bodies.

Other Endocrine Causes

The counter-regulatory hormonal system ensures a continuous supply of glucose to vital organs. Hormones participate either by immediate actions or by chronic (permissive) effects, which may alter the responsiveness of target tissues. Glucagon and adrenaline are the two hormones important for the immediate restoration of the blood glucose concentration, while cortisol and growth hormone have permissive roles. Deficiency of any of these hormones can cause hypoglycemia. However, no human has yet been described with a genetic diagnosis of glucagon or adrenaline deficiency. Congenital hypopituitarism may present with life-threatening hypoglycemia, abnormal serum sodium concentrations, shock, microphallus, jaundice and later growth failure [21]. Congenital hypothyroidism has been reported in a patient presenting with persistent neonatal hypoglycemia but the mechanism is unclear [22]. Primary or secondary adrenal insufficiency is an important cause of hypoglycemia in the newborn.

Metabolic Disorders

A large number of metabolic conditions can present with hypoglycemia (Table 2). These include defects in fatty acid oxidation, glycogenolysis, gluconeogenesis, carnitine metabolism, amino acid metabolism, ketone body synthesis/utilization, organic acidemias, and mitochondrial respiratory chain disorders. Few of the common metabolic conditions are described below.

Fatty Acid Oxidation Disorders (FAOD)

Fatty acid beta-oxidation (FAO) is a key metabolic pathway, disorders of which are one of the most common causes of hypoketotic hypoglycemia. During fasting, FAO supplies ketones as an alternative fuel to glucose for brain, kidney and muscles. In these disorders, hypoglycemia results from underproduction of glucose by the liver associated with above normal consumption of glucose by peripheral tissues due to the incapacity of these tissues to oxidize fatty acids and absence of ketone bodies as alternative fuels.

Presentation of FAOD is either with an acute encephalopathy with a poor ketogenic response, cardiomyopathy, rhabdomyolysis and/or liver disturbance. Typically, neonates present with encephalopathy after poor feeding for 24–36 h. In a large study of 187 patients, diagnosed with FAO disorders between 1977 and 2009, 34 % presented before 2 mo of age [23]. Hypoglycemia was the presenting symptom in 80 % of the newborns. Other associated symptoms were hepatic (89 %), hemodynamic (72 %) and cardiac (75 %) involvement.

Acylcarnitine profile analysis by tandem mass spectrometry is the method of choice for diagnosing these disorders [24]. Urinary organic acid profile will detect increased excretion of dicarboxylic acids and their metabolites, but may be completely normal between attacks.

The most important therapeutic measure in the treatment of FAO disorders is the avoidance of prolonged fasting, especially during an intercurrent illness. In the case of an infectious disease, adequate carbohydrate should be supplied, if necessary by nasogastric feeding or intravenous glucose. High carbohydrate intake not only normalizes the plasma glucose but also efficiently suppresses lipolysis, diminishing the production of toxic metabolites.

Glycogen Storage Disorders

Glycogen storage disorders (GSD) are a group of inherited disorders of glycogen metabolism with abnormal concentration and/or structure of glycogen in different tissues. Liver and muscles are the organs most commonly and seriously involved. The most frequent GSD leading to hypoglycemia is GSD type 1, others being glycogen synthase and amylo-1, 6-glucosidase deficiency.

In GSD type 1a (Glucose-6-phosphatase deficiency), there is impairment of degradation of liver glycogen. The clinical presentation is of profound hypoglycemia few hours after a meal because the enzyme defect not only suppresses glycogenolysis but also the glucose production by the gluconeogenic pathway. Hypoglycemia is accompanied by large hepatomegaly, lactic acidosis, ketosis and hyperuricemia. GSD1b is caused by mutations in the glucose-6-phosphate translocase gene and is characterized by neutropenia in addition to the other features. Earlier, the confirmation of diagnosis required liver biopsy

for enzymatic assay. Nowadays, molecular investigation of glucose-6-phosphatase and glucose-6-phosphate translocase genes can confirm the diagnosis without the need for liver biopsy [25].

Glycogen synthase deficiency (GSD 0) leads to hypoglycemia with a very characteristic profile. Patients present with fasting hypoglycemia accompanied by high levels of blood ketones and low levels of alanine and lactate. Feeding reverses the abnormal biochemical profile often resulting in postprandial hyperglycemia and hyperlactatemia due to inability to trap sufficient glucose as glycogen in the liver [26]. Postprandial hyperglycemia suppresses gluconeogenesis in these patients and cannot be switched back on rapidly enough during fasting to ensure a normal hepatic glucose output. Glucagon administration in the postprandial period causes a rise in blood glucose with a fall in lactate and alanine, but if given after a 12 h fast, similar effect is not seen. The enzyme defect can only be demonstrated in liver, and not in other tissues. Molecular analysis of *GYS2* gene is available to confirm the diagnosis.

Mild ketotic hypoglycemia is also seen in GSD III (amylo-1, 6-glucosidase deficiency). However hypoglycemia usually presents after 2 y of age and is rare in neonates. A glycogen with abnormal structure, *i.e.,* with shorter outer chains, a limit dextrin, accumulates in various organs. A moderate elevation of lactic acid can be observed in the post-absorptive state. Skeletal and cardiac muscle involvement occurs much later and is indicated by elevation of plasma creatine kinase and transaminases. Measurement of debranching enzyme activity and genetic analysis can confirm the diagnosis [27].

Hypoglycemia is either very rare or does not exist in other GSDs.

Gluconeogenic Disorders

Gluconeogenesis is the other major pathway apart from glycogenolysis to prevent blood glucose from dropping too low. Apart from glucose-6-phosphatase deficiency described above, other enzyme defects which disrupt the gluconeogenic pathway include fructose-1, 6-bisphosphatase (FBPase), phosphoenolpyruvate carboxykinase (PEPCK) and pyruvate carboxylase.

FBPase is the rate limiting enzyme of gluconeogenesis, deficiency of which is characterized by episodic spells of

Table 3 Profile of intermediary metabolites and hormones to be collected at the time of hypoglycemia

Sample and indications	Test	Clinical information to help prioritize samples
Blood (If possible, take at least 5 mL) Site an intravenous cannula. Have iv glucose infusion ready and labeled specific sample tubes. After withdrawing the blood, administer iv glucose	Glucose	
	Ketone bodies[a] (3-β hydroxybutyrate and/or acetoacetate)	
	Lactate[a] Pyruvate	Metabolic acidosis, hepatomegaly
	Free fatty acids[a]	Encephalopathy, seizures, respiratory alkalosis, Reye-like presentation
	Amino acids	Metabolic acidosis, hepatomegaly
	Ammonia	Requirement of a high dextrose load, precipitated by high protein load
	Total free carnitine, Acylcarnitine profile	Hepatomegaly, Reye-like presentation
	Insulin[a]/ C-peptide	
	Cortisol[a]/ Growth hormone	Cholestasis, hypernatremia, hypotension, hyperpigmentation, midline defect, micropenis, ambiguous genitalia
	CRP, Infection screen	Unwell
	Urea and electrolytes renal, liver and bone profiles	
	Bicarbonate Blood gas	
	Full blood count Clotting studies	
Urine (5 mL of first urine passed after event) To be kept deep frozen	Reducing substances	
	Ketone bodies	
	Organic acids[a]	Hepatomegaly, recurrent vomiting
	Amino acids	
	Toxicology screen	If suspicion

Contact the laboratory and indicate urgency, especially if limited blood volume available which must be prioritized

[a] Samples only informative if taken during hypoglycemia

hypoglycemia, ketosis, and lactic acidosis during fasting and febrile infectious illnesses [28]. This disease is often fatal in neonatal period and infancy. Controlled diagnostic fast displays a characteristic profile of progressive increase in lactate concentrations with progressive decrease in glucose concentrations. Measurement of FBPase activity in lymphocytes or mutation analysis of *FBP1* gene, which encodes FBPase, will confirm the diagnosis [29].

PEPCK and pyruvate carboxylase deficiency are very rare and the clinical presentation is dominated by other features [30–32]. The entrance of substrates such as glycerol and serine into the gluconeogenic pathway is unaffected in these defects and hence hypoglycemia is not a main feature.

Diagnostic Approach

History

A detailed inquiry for factors predisposing to hypoglycemia is required. It includes details of pregnancy (gestational diabetes, intrauterine growth restriction), delivery (fetal distress, birth asphyxia), birth weight (low birth weight or macrosomia), gestational age (prematurity), rhesus incompatibility, medications (indomethacin) and malabsorption or malnutrition conditions [7, 33, 34]. The relation of the timing of the hypoglycemic episode to the feed may be important as it may give a clue to the underlying causative disorder [33].

Parental consanguinity should be ascertained (metabolic conditions, congenital hyperinsulinism *etc.* are commoner in consanguineous pedigrees) as well as a family history of infantile seizures or deaths and any type of diabetes mellitus [33, 35].

Physical Examination

Weight centile should be noted as macrosomia or IUGR suggest hyperinsulinism as a cause for hypoglycemia. Dysmorphic features (such as macroglossia, ear pits, hemihypertrophy) and organomegaly may suggest Beckwith-Wiedemann syndrome, which can be associated with hyperinsulinism. The presence of undescended testes or micropenis in a male, hyperpigmentation, jaundice and midline defects may indicate hypopituitarism. Ambiguous genitalia might suggest adrenal insufficiency [35]. Hyperventilation, hepatomegaly and jaundice are clues to some metabolic disorders.

Investigations

Precise and fast determination of glycemic status is essential [36]. Bedside reagent test-strip devices are commonly used, but insufficiently reliable, especially at low glucose concentrations. If this method records hypoglycemia, laboratory blood glucose concentration must be determined [37].

Since clinical signs of hypoglycemia are non-specific, infants who seem unwell (poor feeding, respiratory or neurological

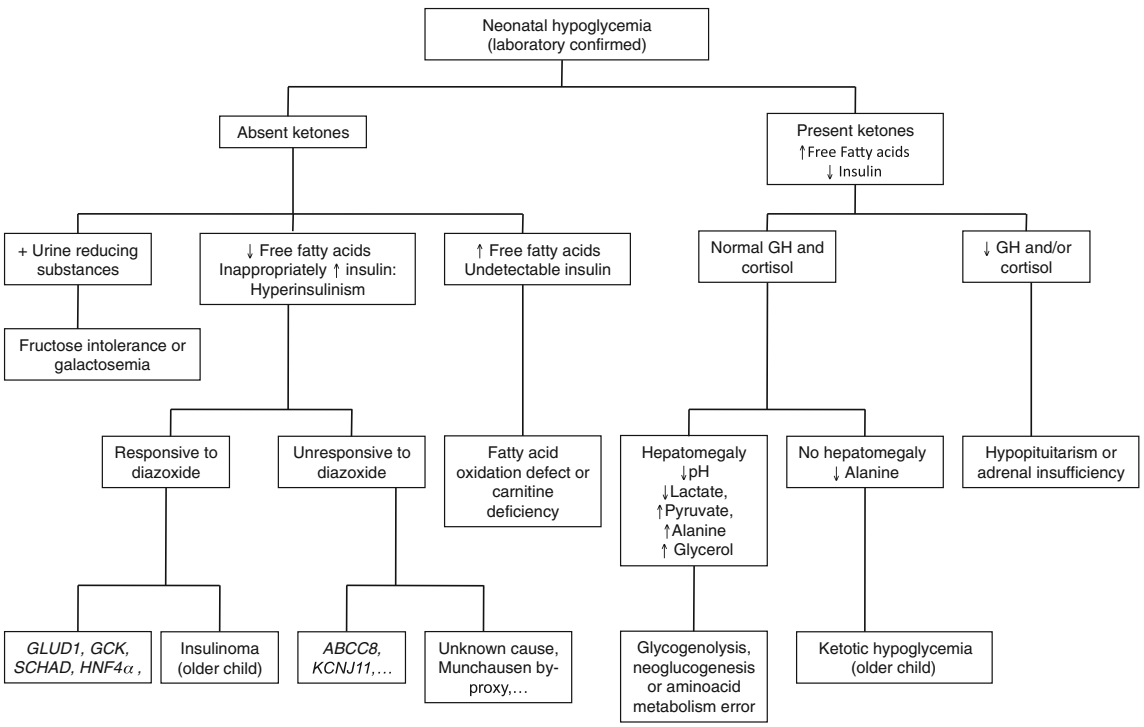

Fig. 2 Diagnostic algorithm for interpretation of clinical and biochemical findings in neonates presenting with hypoglycemia

signs) or are at-risk (Table 1) should be monitored [36]. Standardized screening should be pre-feed, commencing before the second feed and approximately 4-hourly, until at least 2 satisfactory measurements have been achieved and clinical condition remains stable.

Transient hypoglycemia in the first few hours after birth is relatively common, but if it persists and is unresponsive to feeding, further investigations should be undertaken [35].

It is vital to collect the appropriate samples for intermediary metabolites and hormones at the time of a hypoglycemic episode (Table 3) [38]. Depending on these results, further investigations can then be planned [33]. Figure 2 displays a flow diagram to interpret the clinical and biochemical findings.

Treatment

Acute Treatment

Hypoglycemia is a medical emergency. If the neonate is asymptomatic and able to tolerate oral/NG (nasogastric) feeds, increasing the volume and/or frequency of feeds can be tried first as long as the hypoglycemia is not severe. Oral dextrose solutions are not recommended for this purpose as they show no benefit over milk in raising glycemia [36].

If the neonate remains hypoglycemic or the hypoglycemia is severe, an intravenous bolus of 10 % dextrose (2–5 mL/kg) can be administered slowly and always followed by an infusion. While investigations are done to understand the underlying etiology, blood glucose must be kept > 65 mg/dL. It may be necessary to increase the concentration of dextrose infusion and consider central access [35]. Normal glucose requirements in a neonate are between 4 and 6 mg/kg/min, equivalent to the normal hepatic production rate of glucose. Dextrose requirements > 8 mg/kg/min suggests hyperinsulinism and such infants should be transferred to a specialist centre.

Ongoing Management

This will depend on the suspected underlying condition.

Management of Hyperinsulinism

Diazoxide is the first line of treatment and dosage is 5–20 mg/kg/d, administered orally. Given its predisposition to fluid overload, fluid restriction combined with a thiazide diuretic (7–10 mg/kg/d) is required. Diazoxide inhibits insulin release from β-cells by keeping K_{ATP} channels open. In diazoxide unresponsive patients, blood glucose can be stabilized using glucagon and/or octreotide along with high concentration glucose infusions.

Glucagon acts by releasing hepatic glycogen stores and can either be given as a bolus injection or as a continuous infusion (5–10 mcg/kg/h) to stabilize blood glucose levels. Octreotide is a somatostatin analogue that activates potassium channels in β-cell and therefore inhibits insulin release (5–30 mcg/kg/d). There is a long-acting octreotide preparation available to facilitate long-term therapy. Some cases in the literature have been reported to respond to the calcium channel antagonist Nifedipine (0.25–2.5 mg/kg/d) but in authors' experience, it is ineffective [39].

Further management in diazoxide-unresponsive patients is guided by urgent genetic analysis. Those with homozygous or compound heterozygous mutations in *ABCC8* or *KCNJ11* genes display a diffuse form of the disease, whereas a paternally inherited mutation or no mutations may manifest as a focal disease and are potentially curable with resection of focal lesion. In the latter group, positron emission tomography with [18F] fluoro-L-DOPA will confirm and precisely localize the focal lesion to be laparoscopically excised, resulting in cure. In medically unresponsive diffuse disease, a near-total pancreatectomy will be required, being associated with long-term morbidity (diabetes mellitus and pancreatic exocrine insufficiency).

If hypopituitarism is suspected, the child should be referred to a pediatric endocrinologist to assess pituitary function and receive replacement therapy [35]. Metabolic disorders should be dealt with at an experienced centre.

In conclusion, majority of cases of neonatal hypoglycemia are transient and are seen in at-risk neonates. If hypoglycemia is severe, persistent and/or recurrent, investigations are required to understand the underlying condition. Blood samples taken during an episode of hypoglycemia are critical to establish the diagnosis and commence appropriate management.

Conflict of Interest None.

Role of Funding Source None.

References

1. Cornblath M, Hawdon JM, Williams AF, Aynsley-Green A, Ward-Platt MP, Schwartz R, et al. Controversies regarding definition of neonatal hypoglycemia: Suggested operational thresholds. Pediatrics. 2000;105:1141–5.
2. Hussain K, Blankenstein O, De Lonlay P, Christesen HT. Hyperinsulinaemic hypoglycaemia: Biochemical basis and the importance of maintaining normoglycaemia during management. Arch Dis Child. 2007;92:568–70.
3. Collins JE, Leonard JV. Hyperinsulinism in asphyxiated and small-for-dates infants with hypoglycaemia. Lancet. 1984;2:311–3.
4. Shelley HJ, Bassett JM, Milner RD. Control of carbohydrate metabolism in the fetus and newborn. Br Med Bull. 1975; 31:37–43.
5. Arya VB, Flanagan SE, Kumaran A, Shield JP, Ellard S, Hussain K, et al. Clinical and molecular characterisation of hyperinsulinaemic hypoglycaemia in infants born small-for-

gestational age. Arch Dis Child Fetal Neonatal Ed. 2013; doi:10.1136/archdischild-2012-302880.
6. Hussain K, Aynsley-Green A. Management of hyperinsulinism in infancy and childhood. Ann Med. 2000;32:544–51.
7. Aynsley-Green A, Hussain K, Hall J, Saudubray JM, Nihoul-Fékété C, De Lonlay-Debeney P, et al. Practical management of hyperinsulinism in infancy. Arch Dis Child Fetal Neonatal Ed. 2000;82:F98–107.
8. Kapoor RR, Flanagan SE, James C, Shield J, Ellard S, Hussain K. Hyperinsulinaemic hypoglycaemia. Arch Dis Child. 2009;94:450–7.
9. Hussain K. Congenital hyperinsulinism and neonatal diabetes mellitus. Rev Endocr Metab Disord. 2010;11:155–6.
10. Senniappan S, Shanti B, James C, Hussain K. Hyperinsulinaemic hypoglycaemia: Genetic mechanisms, diagnosis and management. J Inherit Metab Dis. 2012;35:589–601.
11. Stanescu DE, Hughes N, Kaplan B, Stanley CA, De León DD. Novel presentations of congenital hyperinsulinism due to mutations in the MODY genes: HNF1A and HNF4A. J Clin Endocrinol Metab. 2012;97:E2026–30.
12. Pinney SE, MacMullen C, Becker S, Lin YW, Hanna C, Thornton P, et al. Clinical characteristics and biochemical mechanisms of congenital hyperinsulinism associated with dominant KATP channel mutations. J Clin Invest. 2008;118:2877–86.
13. Rahier J, Guiot Y, Sempoux C. Persistent hyperinsulinaemic hypoglycaemia of infancy: A heterogeneous syndrome unrelated to nesidioblastosis. Arch Dis Child Fetal Neonatal Ed. 2000;82:F108–12.
14. Otonkoski T, Näntö-Salonen K, Seppänen M, Veijola R, Huopio H, Hussain K, et al. Noninvasive diagnosis of focal hyperinsulinism of infancy with [18F]-DOPA positron emission tomography. Diabetes. 2006;55:13–8.
15. Hsu BY, Kelly A, Thornton PS, Greenberg CR, Dilling LA, Stanley CA. Protein-sensitive and fasting hypoglycemia in children with the hyperinsulinism/hyperammonemia syndrome. J Pediatr. 2001;138:383–9.
16. Bahi-Buisson N, Roze E, Dionisi C, Escande F, Valayannopoulos V, Feillet F, et al. Neurological aspects of hyperinsulinism-hyperammonaemia syndrome. Dev Med Child Neurol. 2008;50:945–9.
17. Kapoor RR, Locke J, Colclough K, Wales J, Conn JJ, Hattersley AT, et al. Persistent hyperinsulinemic hypoglycemia and maturity-onset diabetes of the young due to heterozygous HNF4A mutations. Diabetes. 2008;57:1659–63.
18. Cuesta-Muñoz AL, Huopio H, Otonkoski T, Gomez-Zumaquero JM, Näntö-Salonen K, Rahier J, et al. Severe persistent hyperinsulinemic hypoglycemia due to a de novo glucokinase mutation. Diabetes. 2004;53:2164–8.
19. Bohles H, Sewell AA, Gebhardt B, Reinecke-Luthge A, Kloppel G, Marquardt T. Hyperinsulinaemic hypoglycaemia—leading symptom in a patient with congenital disorder of glycosylation Ia (phosphomannomutase deficiency). J Inherit Metab Dis. 2001;24:858–62.
20. Munns CF, Batch JA. Hyperinsulinism and Beckwith-Wiedemann syndrome. Arch Dis Child Fetal Neonatal Ed. 2001;84:F67–9.
21. Bell JJ, August GP, Blethen SL, Baptista J. Neonatal hypoglycemia in a growth hormone registry: Incidence and pathogenesis. J Pediatr Endocrinol Metab. 2004;17:629–35.
22. Kurtoğlu S, Tutuş A, Aydin K, Genç E, Caksen H. Persistent neonatal hypoglycemia: An unusual finding of congenital hypothyroidism. J Pediatr Endocrinol Metab. 1998;11:277–9.
23. Baruteau J, Sachs P, Broué P, Brivet M, Abdoul H, Vianey-Saban C, et al. Clinical and biological features at diagnosis in mitochondrial fatty acid beta-oxidation defects: A French pediatric study of 187 patients. J Inherit Metab Dis. 2012. doi:10.1007/s10545-012-9542-6.
24. Millington DS, Kodo N, Norwood DL, Roe CR. Tandem mass spectrometry: A new method for acylcarnitine profiling with potential for neonatal screening for inborn errors of metabolism. J Inherit Metab Dis. 1990;13:321–4.
25. Froissart R, Piraud M, Boudjemline AM, Vianey-Saban C, Petit F, Hubert-Buron A, et al. Glucose-6-phosphatase deficiency. Orphanet J Rare Dis. 2011;6:27.
26. Orho M, Bosshard NU, Buist NR, Gitzelmann R, Aynsley-Green A, Blümel P, et al. Mutations in the liver glycogen synthase gene in children with hypoglycemia due to glycogen storage disease type 0. J Clin Invest. 1998;102:507–15.
27. Mili A, Ben Charfeddine I, Mamai O, Abdelhak S, Adala L, Amara A, et al. Molecular and biochemical characterization of Tunisian patients with glycogen storage disease type III. J Hum Genet. 2012;57:170–5.
28. Pagliara AS, Karl IE, Keating JP, Brown BI, Kipnis DM. Hepatic fructose-1,6-diphosphatase deficiency. A cause of lactic acidosis and hypoglycemia in infancy. J Clin Invest. 1972;51:2115–23.
29. van den Berghe G. Disorders of gluconeogenesis. J Inherit Metab Dis. 1996;19:470–7.
30. Clayton PT, Hyland K, Brand M, Leonard JV. Mitochondrial phosphoenolpyruvate carboxykinase deficiency. Eur J Pediatr. 1986; 145:46–50.
31. Hommes FA, Bendien K, Elema JD, Bremer HJ, Lombeck I. Two cases of phosphoenolpyruvate carboxykinase deficiency. Acta Paediatr Scand. 1976;65:233–40.
32. Garcia-Cazorla A, Rabier D, Touati G, Chadefaux-Vekemans B, Marsac C, de Lonlay P, et al. Pyruvate carboxylase deficiency: Metabolic characteristics and new neurological aspects. Ann Neurol. 2006;59:121–7.
33. Hussain K. Investigations for neonatal hypoglycaemia. Clin Biochem. 2011;44:465–6.
34. Lang TF. Update on investigating hypoglycaemia in childhood. Ann Clin Biochem. 2011;48:200–11.
35. Peters CJ, Hindmarsh PC. Management of neonatal endocrinopathies—best practice guidelines. Early Hum Dev. 2007;83:553–61.
36. Deshpande S, Ward PM. The investigation and management of neonatal hypoglycaemia. Semin Fetal Neonatal Med. 2005;10:351–61.
37. Committee on Fetus and Newborn, Adamkin DH. Postnatal glucose homeostasis in late-preterm and term infants. Pediatrics. 2011;127:575–9.
38. Cook P, Walker V. Investigation of the child with an acute metabolic disorder. J Clin Pathol. 2011;64:181–91.
39. Muller D, Zimmering M, Roehr CC. Should nifedipine be used to counter low blood sugar levels in children with persistent hyperinsulinaemic hypoglycaemia? Arch Dis Child. 2004;89:83–5.