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Genetic Disorders Leading to Hypoglycaemia

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Abstract

Hypoglycaemia is common in clinical practice and can be a manifestation of many underlying conditions. It is a biochemical finding and not a diagnosis. Therefore an understanding of the molecular mechanisms that lead to hypoglycaemia is important. At a genetic level, hypoglycaemia can be due to many different genetic disorders both metabolic and endocrine. Some of these genetic disorders present with severe and profound hypoglycaemia in the newborn period yet others can be mild and subtle. Recent advances in the fields of genomics and molecular biology have begun to give fundamental novel insights into the mechanisms regulating blood glucose levels. This state of the art review article will provide an in-depth knowledge into the genetic mechanisms that lead to hypoglycaemia.

Keywords: Hypoglycaemia; Glucose; Hyperinsulinism; Gluconeogenesis; Glycogenolysis

Introduction

An overview of glucose physiology

Glucose is the principal substrate for energy metabolism and disorders that affect its availability or use can result in hypoglycaemia. A normal blood glucose level is maintained by the interplay of glucose production and glucose utilisation. The key sources of glucose production include glucose ingestion from the diet and the adaptive metabolic processes of glycogenolysis and gluconeogenesis [1] (Figure 1).

Endogenous glucose supply depends on the breakdown of glycogen stores for the first a few hours after birth, followed by synthesis of glucose from lactate, glycerol and amino acids. When glucose levels begin to decline during fasting states, hormonal and metabolic pathways are triggered to raise the blood glucose level. Hormonal equilibrium is maintained by the appropriate response of insulin and counter-regulatory hormones such as epinephrine, glucagon, growth hormone and cortisol. The central nervous system integrates the counter-regulatory hormonal responses, and coordinates the neuroendocrine, autonomic and behavioural responses to hypoglycaemia [2].

Insulin has numerous effects on glucose physiology. It suppresses hepatic glycogenolysis, gluconeogenesis, lipolysis and ketogenesis. It also causes the translocation of glucose transporters (GLUTs) in muscle and adipose tissue to increase their glucose uptake [3]. Epinephrine inhibits insulin secretion while decreasing insulin action, stimulates hepatic and renal glucose production and facilitates lipolysis [4]. Glucagon raises glucose levels by activating glycogenolysis and gluconeogenesis [5]. Cortisol and growth hormone regulate blood glucose levels by increasing glucose production, decreasing glucose utilization and promoting lipolysis [6,7].

During fasting, glucose is generated through the activation of glycogenolysis. As fasting progresses, plasma insulin levels decrease while glucagon levels increase, stimulating glycogenolysis. When glycogen stores in the liver are exhausted, gluconeogenesis becomes the predominant source of glucose production. Lactate, glycerol, pyruvate and amino acids (such as alanine and glutamine) are the main gluconeogenic substrates used for glucose production [8] (Figure 1).

Fasting also generates large amounts of acetyl-CoA through β-oxidation of fatty acids (Figure 2). The accumulated acetyl-CoA can either undergo ketogenesis or enter the Krebs cycle. Active long-chain fatty acids (acyl-CoA) need carnitine as a transport to enter the mitochondrial membrane. Carnitine palmitoyltransferase-I (CPT-I) present in the outer mitochondrial membrane combines with long-chain acyl-CoA to form acylcarnitine, which penetrates the inner membrane of mitochondria to gain access for β-oxidation. The acylcarnitine then reacts with CoA, catalysed by carnitine palmitoyltransferase-II (CPT II). Acyl-CoA is reformed in the mitochondrial matrix and carnitine is liberated. Fatty acid oxidation produces ketone bodies, an alternate energy fuel [8,9].

Insulin is the key hormone involved in regulating the blood glucose level. Glucose and other substrates, such as amino acids, by raising the intracytosolic ATP/ADP ratio in the β-cell of pancreas cause insulin secretion. In the β-cell, rise in ATP inhibits the plasma membrane sulphonylurea receptor1 (SUR1), leading to a sequence of events; closure of the K_{ATP} channel, depolarization of the cell membrane and calcium influx through voltage-gated calcium channels, resulting in release of insulin by exocytosis from the storage granules [10].

Historical perspective

In 1954 Irvine McQuarrie described 'idiopathic hypoglycaemia of infancy' in his presidential address to the American Paediatric Society [11]. Cochrane et al. (1956), described leucine sensitive hypoglycaemia [12]. Both the above authors identified familial cases and implied a genetic basis for hypoglycaemia. Yalow and Berson published the first

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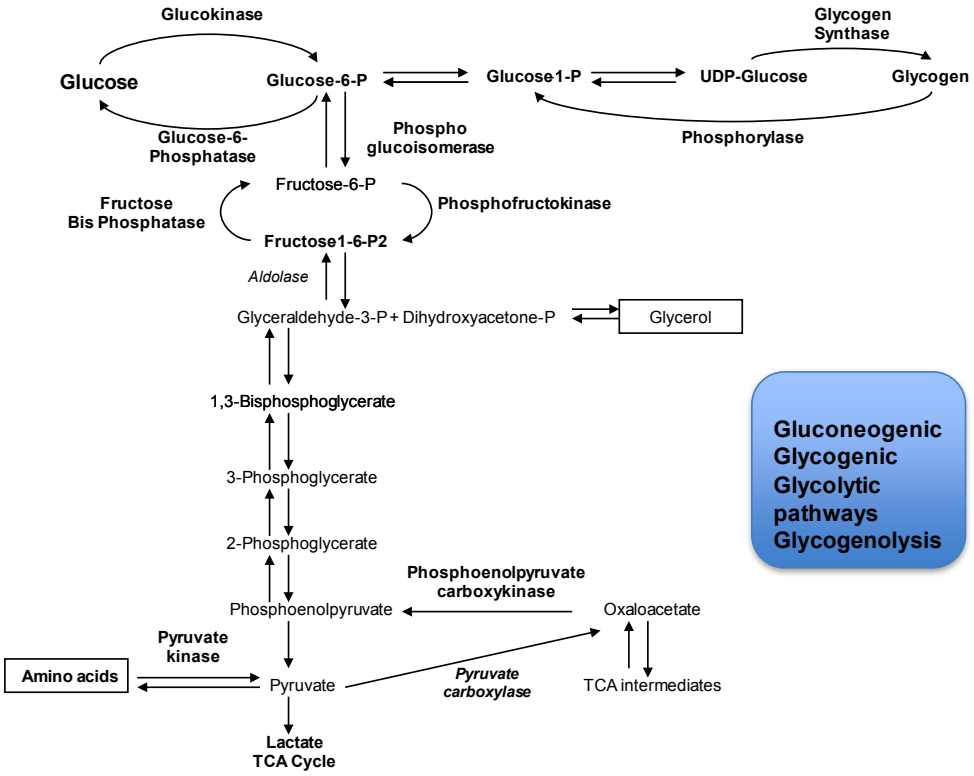

Figure 1: The gluconeogenic, glycolytic, glycogenolysis and glycogen synthesis pathways are shown. Glycerol and amino acids entering the gluconeogenic pathway are also shown.

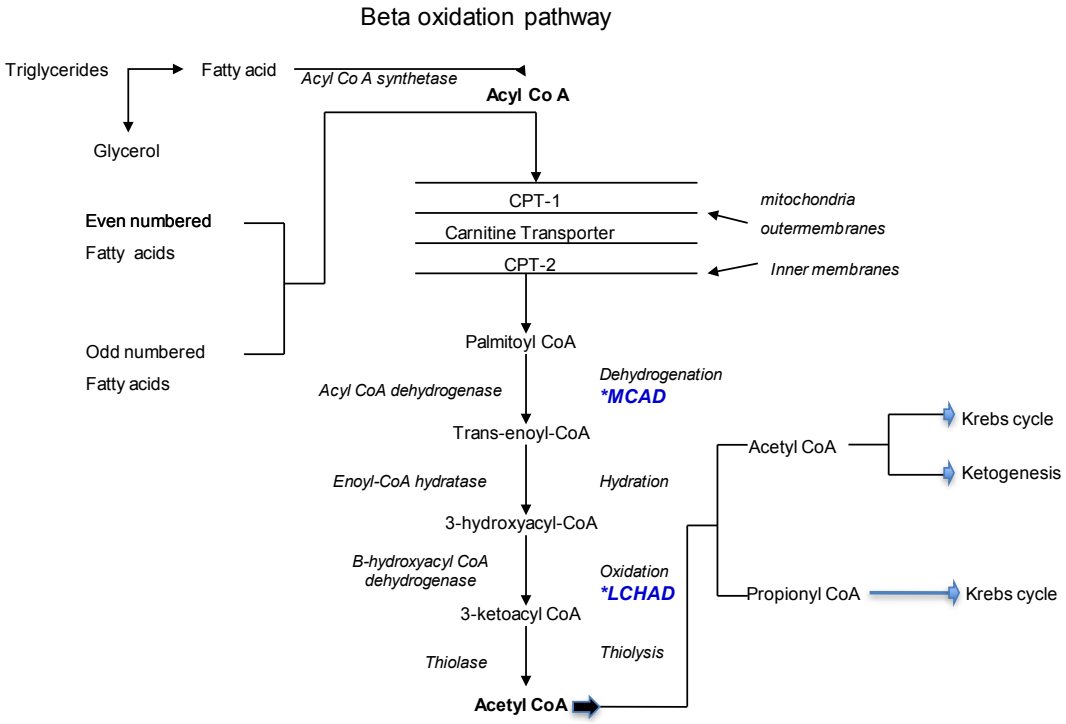

Figure 2: β-oxidation of fatty acids. Role of carnitine in the transport of fatty acids – Carnitine shuttle. Acyl-CoA is converted to acetyl-CoA through dehydrogenation, hydration, oxidation and thiolysis. Acetyl-CoA can enter the Krebs cycle or can lead to ketogenesis. CPT-I, Carnitine palmitoyltransferase-I, CPT-2 – Carnitine palmitoyltransferase -2, MCAD - Medium-chain Acyl-Co A dehydroxgenase, LCHAD - Long - chain3-hydroxyacyl-CoA dehydrogenase.

application of the insulin radioimmunoassay and showed that leucine sensitive hypoglycaemia was due to insulin [13]. Drash and Wolf in 1965 used diazoxide successfully to control hypoglycaemia [14]. The terminology, nesidioblastosis was replaced by idiopathic hypoglycaemia of infancy in 1970's. Pathologists described nesidioblastosis to be a normal feature of the pancreas in neonates and young infants and paediatricians later abandoned this terminology [15]. The genetic basis of hyperinsulinaemic hypoglycaemia (HH) was first reported in early 1990's [16,17]. Today mutations in nine different genes expressed in the β-cells of the pancreas have been implicated in the pathophysiology of different forms of HH [18].

Outline of the genetic mechanisms leading to hypoglycaemia

Defects in a large number of endocrine and metabolic pathways can lead to hypoglycaemia. Table 1 is a summary of the known genetic causes of hypoglycaemia. Each of these causes is discussed in more detail below.

Congenital hyperinsulinism (CHI): CHI is a cause of HH in neonates and infants. CHI is a genetically heterogeneous disease characterised by unregulated insulin secretion from pancreatic β-cells. In the face of hypoglycaemia, infants with CHI have inappropriately elevated serum insulin levels, low ketone bodies, and low fatty acids and show a glycaemic response to glucagon. Infants with CHI typically need a glucose infusion rate of more than 8 mg/kg/min to maintain normoglycaemia. In patients with CHI mutations in the key genes (*ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, HNF4A, HNF1A and UCP2*) regulating insulin secretion have been identified [18]. Integrity of the pancreatic β-cell ATP sensitive potassium (K_{ATP}) channel depends on the interactions between the pore-forming inward rectifier potassium channel subunit (KIR6.2) and the regulatory subunit sulfonylurea receptor 1 (SUR1). The *ABCC8* and *KCJN11* genes (both localized to chromosome 11p15.1) encode the two components of K_{ATP} channel and most of the severe forms of CHI are due to recessively inactivating mutations of these genes [19].

Deficiency of counter-regulatory hormones

Combined pituitary hormone deficiency (CPHD)/congenital hypopituitarism: A diagnosis of CPHD is made when a patient has

Hyperinsulinism	**Congenital Hyperinsulinism**	[18,19]
Deficiency of counter regulatory hormones	Congenital hypopituitarism ACTH deficiency Isolated GH deficiency Congenital glucagon deficiency Cortisol deficiency Congenital Adrenal hyperplasia Adrenal Hypoplasia Congenita Familial Glucocorticoid deficiency Dopamine β-hydroxylase deficiency	[22-24] [25-27] [28] [29] [30,31] [32-36] [37] [38] [39,40]
Disorders of hepatic glycogen synthesis and release	GSD I – Von Gierke Disease GSD type III GSD VI (Hers Disease) GSD IX b, c GSD 0	[42,43] [44,45] [46] [48,49] [51]
Disorders of fructose metabolism	Hereditary Fructose intolerance	[53]
Disorders of gluconeogenesis	Fructose-1, 6-bisphosphatase deficiency Phosphoenolpyruvate carboxykinase deficiency (PEPCK) Pyruvate carboxylase deficiency	[55] [57,58] [60]
Disorders of galactose metabolism	Galactosaemia	[62-64]
Hereditary Defects in Amino Acid Metabolism	Maple Syrup Urine Disease Propionic acidaemia Methylmalonic acidaemia Tyrosinaemia	[66,67] [69] [68,70] [72]
Hereditary Defects in Fatty Acid Metabolism	Defects in β-oxidation MCAD deficiency LCHAD deficiency SCHAD deficiency	 [75] [76] [78]
Disorders of Carnitine Metabolism	Primary Carnitine deficiency (CPT- I) deficiency CACT deficiency (CPT-II) deficiency	[80] [82] [83] [84,85]
Disorders of mitochondrial metabolism	ETF deficiency / ETFDH deficiency	[86]
Disorders of Ketone body synthesis and utilisation	HMG Co A synthase deficiency HMG Co A lyase deficiency β-ketothiolase deficiency SCOT deficiency	[89] [90] [92] [94,95]
Syndromes Associated with Hypoglycaemia	Beckwith-Wiedemann Syndrome (BWS) Laron syndrome Glucocorticoid Resistance syndrome Leprechaunism Rabson-Mendenhall syndrome Sotos syndrome Timothy syndrome	[96] [98] [99] [100] [100] [104] [105]
Miscellaneous disorders	Defects in Citrin metabolism Activating AKT2 mutations	[108] [110]

Table 1: Genetic causes of hypoglycaemia.

multiple pituitary hormone deficiency. CPHD may also occur as a component of one of several mid-line defect syndromes like Septo-optic Dysplasia (SOD). Hypoglycaemia is common in the newborn period due to deficiency of the counter-regulatory hormones such as Growth Hormone (GH) and adrenocorticotropic hormone (ACTH) [6,7,20]. CPHD presents with hypoglycaemia, hypothyroidism and microphallus in a neonate [21]. The *PIT-1 gene* on chromosome 3p11.2 is a pituitary-specific transcription factor necessary for the development of somatotroph, lactotroph, and thyrotroph lineages [22]. Mutations of *PIT-1* are associated with deficiencies of GH, prolactin, and TSH. The *LHX4* gene on chromosome 1q25.2 encodes the *LHX4* protein, which is needed for the expression of other pituitary transcription factors including *LHX3* (gene on chromosome 9q34.3). Mutations of *LHX4* lead to autosomal dominant CPHD. The *PROP-1* protein has both DNA binding and transcription activation ability and its expression allows pituitary ontogenesis. Mutations of *PROP-1* (gene on chromosome 5q35.3) are also associated with CPHD. Homozygous inactivating mutations in *HESX1 gene* (chromosome 3p14.3) produce a complex phenotype with pituitary hypoplasia that resembles septo-optic dysplasia [23,24].

ACTH deficiency: Isolated ACTH deficiency is a rare disorder causing severe hypoglycaemia due to secondary adrenal insufficiency with low or absent cortisol and normal levels of other pituitary hormones. It can present in infancy following specific genetic mutations, pro-opiomelanocortin (*POMC* on chromosome 2p23.3) or T-box transcription factor (*TPIT*) mutations. Both *POMC* and *TPIT* mutations are inherited as autosomal recessive (AR) traits. Complete loss of *POMC*-derived ACTH occurs with loss-of-function mutations of the *POMC* gene, whereas inactivating *TPIT* mutations disrupt terminal differentiation of corticotropic cells specialized in *POMC* gene expression resulting in severe hypoglycaemia and seizures [25-27].

Isolated GH deficiency: Genes involved in the aetiology of isolated GH deficiency include those that encode GH, growth-hormone-releasing hormone receptor (GHRHR) and transcription factor SOX3 [28]. GH deficiency causes hypoglycaemia due to the absence of its counter-regulatory role in glucose homeostasis.

Congenital glucagon deficiency: There are few clinical reports of glucagon deficiency due to absence of α-cells in the pancreas [29]. Being a counter-regulatory hormone, glucagon deficiency might result in severe hypoglycaemia, however no human case of genetically proven glucagon deficiency has yet been reported.

Cortisol deficiency: Primary adrenal insufficiency or Addison's disease can occur in isolation or as part of a syndrome with hypoglycaemia. Type 1 autoimmune polyendocrinopathy syndrome (APS1: adrenocortical insufficiency, candidiasis, ectodermal dysplasia) has a childhood onset and is recessively inherited. APS1 is caused by mutation in the autoimmune regulator gene (*AIRE*) on chromosome 21q22.3. Isolated autoimmune Addison's disease and type 2 autoimmune polyendocrinopathy syndrome (APS2: adrenocortical insufficiency, thyroid disease, type 1 diabetes) have complex multigenic inheritance. The major susceptibility loci for APS2 are within the MHC region of chromosome 6p21, *CTLA4* (2q33) and *PTPN22* (1p13). In recent years additional loci in *CYP27B1, FCRL3 and CIITA* have been reported [30,31].

Congenital adrenal hyperplasia (CAH): CAH encompasses a group of AR disorders, characterised by deficiency of enzymes involved in the synthesis of cortisol and aldosterone. Clinical features include hyponatraemia, hypotension, hypoglycaemia and ambiguous genitalia. The most common enzyme deficiencies are 21-hydroxylase and 11β-hydroxylase. Genetic mutations are identified in the gene locus/chromosome as shown in [32-36].

Adrenal hypoplasia congenita (AHC): AHC is a genetically inherited combined glucocorticoid and mineralocorticoid deficiency with hypogonadotropic hypogonadism. Clinical signs and symptoms in infants with AHC include failure to thrive, vomiting, dehydration, and hyperpigmentation. Salt wasting (hyponatraemia), hyperkalaemia, metabolic acidosis, and hypoglycaemia are common. AHC affects primarily boys and is caused by mutation of the *DAX1* (*NR0B1*) gene on chromosome Xp21.2 [37].

Familial glucocorticoid deficiency (FGD): FGD is an AR inherited isolated deficiency of glucocorticoids with elevated ACTH and normal aldosterone and renin levels. Pathologic evaluation of children affected with this disorder reveals that the zona glomerulosa of the adrenal glands is well preserved. The zona fasciculata and zona reticularis are markedly atrophic. Common clinical presentations of FGD include hypoglycaemia, seizures and increased pigmentation. FGD can be caused by mutations in the genes *MC2R* (FGD type 1), *MRAP* (FGD type 2), *STAR and MCM4* mapped on chromosomes 18p11.21, 21q22.11, 8p11.23, 8q11.21 respectively [38].

Dopamine β-hydroxylase deficiency: Dopamine β-hydroxylase (DβH) deficiency is a very rare form of AR inherited primary autonomic failure, characterised by a complete absence of noradrenaline and adrenaline and increased plasma dopamine levels [39]. Symptoms can begin at birth with hypotension, hypothermia and hypoglycaemia. Older children have reduced ability to exercise because of autonomic maladaptation with exertion. This rare genetic disease is caused by mutations in the *DBH* gene, mapped to chromosome 9q34, encoding this key enzyme in noradrenaline synthesis [40].

Disorders of hepatic glycogen synthesis and release

The Glycogen Storage Disease (GSD) types I, III, VI, IX and 0 affect glucose homeostasis and presents typically with fasting hypoglycaemia and hepatomegaly [41]. Table 2 summarise the GSD's which cause hypoglycaemia.

GSDI-Von Gierke Disease: GSD type Ia is the most common and severe form of glycogenosis. In GSD Ia, glucose-6-phosphatase (G-6-Pase) is defective whereas in GSD Ib translocase that transports glucose-6-phosphate across the microsomal membrane is defective. Patients with GSD Ia present clinically with hepatomegaly and seizures and the biochemistry is characterised by hypoglycaemia, lactic acidosis, hyperuricaemia and hyperlipidaemia. Deficiency of G-6-Pase blocks the final steps of glycogenolysis and gluconeogenesis [41]. GSD Ia is caused by homozygous or compound heterozygous mutation in the *G6PC* gene, which encodes glucose-6-phosphatase on chromosome 17q21, whereas Ib is due to mutations in the *SLC37A4* gene located on chromosome 11q23.3. GSD Ia and b are AR disorders [42]. Carrier detection and prenatal diagnosis are possible for GSD type Ia [43].

GSD type III: GSD type III is caused by deficiency of glycogen debranching enzyme. The enzymes α(1→4)→α(1→4) glucan transferase and amylo-α(1→6)-glucosidase together with phosphorylase, are vital in degradation of glycogen. In GSD IIIa, both liver and muscle debrancher enzymes are deficient but in IIIb, liver enzymes alone are deficient. The debrancher enzyme converts glycogen to glucose-1,6-phosphate. Deficiency leads to liver disease, hypoglycaemia and seizures [41]. GSD III is caused by homozygous or compound heterozygous mutation in the gene encoding the glycogen debrancher

Disorders	Enzyme deficienc	Clinical features	Gene/locus Chromosome	
GSDIa/ Von Gierke	Glucose-6-phosphatase	Severe hypoglycaemia, Hepatomegaly, elevated lactate, lipids	G6PC gene 17q21	[42]
GSD Ib	Glucose-6-phosphate translocase	Same as GSD Ia with neutropenia and impaired neutrophil function	SLC37A4 11q23.3	[43]
GSD IIIa/Cori	Amylo,1,6 glucosidase (Liver and muscle)	Hepatomegaly, muscle weakness, hypoglycaemia, hyperlipidaemia	AGL 1p21.2	[44]
GSD IIIb	Amylo,1,6 glucosidase (Liver only)	Hepatomegaly, hypoglycaemia, hyperlipidaemia	AGL 1p21.2	[44]
GSDVI/Hers disease	Liver phosphorylase	Hepatomegaly and mild to moderate hypoglycaemia	PYGL 14q22.1	[46]
GSD IXb	Phosphorylase kinase (Liver and muscle)	Hepatomegaly and mild hypoglycaemia on prolonged fasting	PHKB 16q12.1	[48,49]
GSD IXc	Phosphorylase kinase deficiency, Liver/Testis	Hepatomegaly, recurrent hypoglycaemia, Liver cirrhosis	PHKG2 16p11.2	[48,49]
GSD 0	Glycogen synthetase deficiency	Hypoglycaemia and hyperketonaemia	GYS2 12p12.1	[51]

Table 2: Glycogen storage disorders presenting with hypoglycaemia.

enzyme (*AGL*) on chromosome 1p21.2 and is an AR inherited disease [44]. Using mutation analysis or DNA based linkage prenatal diagnosis of GSD III can be made [45].

GSD VI (Hers Disease): Hers disease is a rare form of GSD due to phosphorylase deficiency. Liver glycogen phosphorylase catalyses the rate limiting step in glycogenolysis. In patients with Hers disease, defective liver phosphorylase results in growth retardation, hepatomegaly and hypoglycaemia [41]. The phosphorylase enzyme is found in the liver and in red blood cells. GSD VI is caused by homozygous or compound heterozygous mutation in the *PYGL* gene on chromosome 14 and is an AR inherited disease [46].

GSD IXb, c: GSD IX is due to phosphorylase kinase deficiency. A cascade of enzymatic reactions involving adenylate cyclase, cyclic AMP dependent protein kinase and phosphorylase kinase activates phosphorylase, the rate-limiting enzyme of glycogenolysis. This cascade of reactions is stimulated primarily by glucagon. Both GSD IXb and c forms present with hepatomegaly, hypoglycaemia, liver dysfunction, fasting ketosis and hypotonia [41,47]. GSD IXb and c are AR inherited and is caused by mutation in the *PHKB* and *PHKG2* genes encoding phosphorylase kinase on chromosome 16 [48,49].

GSD 0: Glycogen synthetase deficiency appears in childhood with fasting hypoglycaemia and ketosis. In patients with GSD disease type 0, fasting hypoglycaemia occurs within a few hours after a meal because of the limited stores of hepatic glycogen. Feeding relieves symptoms but postprandial hyperglycaemia and hyperlacticacidaemia occurs [41]. Unlike other forms of GSD, moderately decreased glycogen stores in the liver characterise this type of GSD. Symptoms range from asymptomatic hyperglycaemia to recurrent hypoglycaemic seizures [50]. AR mode of inheritance has been described in GSD 0 and the gene is mapped to *GYS2* locus on chromosome 12 [51].

Disorders of Fructose Metabolism

Hereditary Fructose Intolerance (HFI)

Unlike glucose, fructose can enter the cells in the absence of insulin via the fructose transporter GLUT5. The liver enzyme fructokinase phosphorylates fructose to fructose-1-phosphate (F-1-P), which undergoes hydrolysis (by Aldolase B) to form dihydroxyacetone phosphate (DHAP) and glyceraldehyde. Glyceraldehyde then undergoes phosphorylation to glyceraldehyde-3-phosphate. The latter and DHAP in higher concentration enter the gluconeogenic pathway through fructose-1-6 bisphosphate by the action of aldolase A (Figure 3). Aldolase B is an essential enzyme in the process of gluconeogenesis. The absence of this enzyme explains the clinical hypoglycaemia in HFI. Deficiency of aldolase B leads to accumulation of F-1-P [52]. Symptoms begin with ingestion of fructose with jaundice, vomiting, lethargy, irritability, convulsions with severe hypoglycaemia. HFI is an AR disease caused by impaired functioning of human liver aldolase B due to mutations in *ALDOB* gene on chromosome 9q22.3. At least 54 subtle/point mutations and two large intragenic deletions have been found in the *ALDOB* gene [53].

Disorders of Gluconeogenesis

Fructose-1,6-bisphosphatase deficiency

Fructose-1,6-bisphosphatase catalyses the conversion of fructose-1,6-bisphosphate to fructose-6-phosphate. A deficiency of fructose-1,6-bisphosphatase impairs the formation of glucose from all gluconeogenic precursors. Patients present biochemically with fasting hypoglycaemia and lactic acidosis. Diagnosis can be confirmed by measuring the enzyme activity in liver biopsy tissue. Incidence of fructose-1,6-bisphosphatase deficiencies is 1 in 20,000 live births [54]. The gene coding for fructose-1,6-bisphosphatase (*FBP1*) is located on chromosome 9q22; mutations are characterized, making the carrier detection and prenatal diagnosis possible [55].

Phosphoenolpyruvate carboxykinase deficiency (PEPCK)

PEPCK deficiency is a rare disease. PEPCK is an essential enzyme in gluconeogenesis which catalyzes the conversion of oxaloacetate to phosphoenolpyruvate. In the face of PEPCK deficiency patient presents with hypoglycaemia, lactic acidaemia, hepatomegaly, hypotonia and developmental delay [56]. Diagnosis can be made on the basis of reduced PEPCK activity in liver. PEPCK deficiency is both a mitochondrial and cytosolic enzyme deficiency, encoded by 2 distinct genes on chromosome 14q11.2-q12 (*PCK2* gene) and 20q13.31 (*PCK1*gene) respectively [57,58].

Pyruvate carboxylase deficiency

Pyruvate, lactate and alanine enter the first enzymatic step of gluconeogenesis in the presence of pyruvate carboxylase. Clinical features of pyruvate carboxylase deficiency include hypoglycaemia severe developmental delay, necrotising encephalopathy, and death in early infancy. Biochemical manifestations include metabolic acidosis, ketonuria, and elevated plasma concentrations of lactate, pyruvate, and

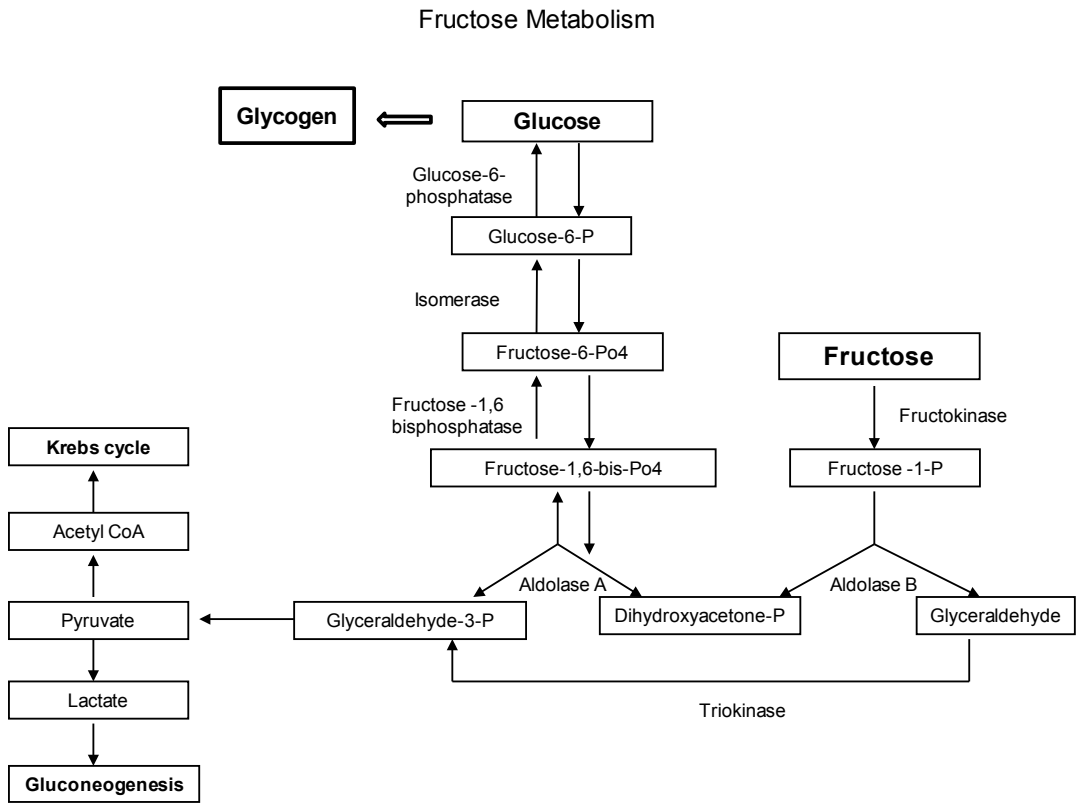

Figure 3: Diagram showing the metabolism of fructose to glycogen in the liver. Fructose can enter the Krebs cycle or gluconeogenic pathway.

alanine. The long-term prognosis is poor [59]. Pyruvate carboxylase deficiency is caused by missense mutation in *PC* gene on chromosome 11q13.2 [60].

Disorders of Galactose Metabolism

Galactosaemia

Lactose, a disaccharide present in the milk, is hydrolysed by intestinal lactase to glucose and galactose. Galactokinase phosphorylates galactose to galactose-1-phosphate, which in turn forms UDP-galactose in the presence of galactose-1-phosphate uridyltransferase (GALT). Finally epimerase interconverts UDP galactose to UDP glucose. Galactosaemia cause severe hypoglycaemia in the neonatal period following ingestion of milk feeds. Classic form of galactosaemia designates complete GALT deficiency and characterized by Jaundice, hepatomegaly, vomiting, seizures, cataracts and mental retardation. Epimerase deficiency has two distinct forms of galactosaemia: benign form where the enzyme is deficient in the erythrocytes and leukocytes whereas in the severe form the enzyme deficiency is generalized and they resemble GALT deficient type of galactosaemia [61].

All three forms of Galactosaemia are AR inherited. Galactokinase deficiency is caused by mutations in the *GALK1* gene on chromosome 17q25.1 [62] whereas mutations in *GALT* gene on chromosome 9p13.3 cause *GALT* deficient type of galactosaemia [63]. Epimerase deficient galactosaemia is due to homozygous or compound heterozygous mutation in *GALE* gene on chromosome 1p36. Carrier testing and prenatal diagnosis can be done by direct enzyme analysis of chorionic villi or amniocytes [64].

Hereditary Defects in Amino Acid Metabolism

Maple Syrup Urine Disease (MSUD)

MSUD, propionic acidaemia and methylmalonic acidaemia are due to defects in degradation of branched chain amino acids causing accumulation of organic acids. Human branched chain α-ketoacid dehydrogenase (BCKDH) causes decarboxylation of leucine, isoleucine and valine using thiamine pyrophosphate as a coenzyme. This mitochondrial enzyme complex has for subunits: E1α, E1β, E2 and E3. A deficiency of this enzyme causes MSUD and inhibits the entry of the branched chain amino acids into gluconeogenesis through Krebs cycle. Affected Infants develop vomiting, lethargy, hypoglycaemia, metabolic acidosis and seizures by first week of life [65]. The urine smell of maple syrup, elevated plasma and urine levels of branch chain amino acids will make the diagnosis. The prevalence is estimated at 1 in 185,000 live births. MSUD is an AR inherited disorder, mutations in *E1α, E1β, E2* and *E3* genes with loci on chormosome19q13.1, 6q14.1, 1p21.2 and 7q31-q32 respectively, cause the disease [66,67].

Propionic acidaemia

Propionic acid is an intermediate metabolite of isoleucine, valine, threonine and methionine. These amino acids are carboxylated to methylmalonic acid by the mitochondrial enzyme propionyl CoA carboxylase (subunits α and β) in presence of cofactor biotin; deficiency blocks the entry of these amino acids into gluconeogenic pathway. Clinical features are similar to MSUD. In addition to hypoglycaemia, acidosis and ketosis these patients will have hyperglycinaemia [68]. Incidence varies from 1:2000 to 1:5000 live births. Propionic acidaemia is an AR inherited disorder following mutations in genes for α (*PCCA*

gene) and β (*PCCB* gene) subunits mapped to the chromosomes 13q32 and 3q21-q22 respectively [69].

Methylmalonic acidaemia

Methylmalonic acid is derived from the propionic acid. Methylmalonic acid is converted to succinic acid by enzyme, methylmalonyl CoA mutase in presence of coenzyme adenosylcobalamin, deficiency of which inhibits amino acids from entering the gluconeogenic pathway. Its clinical features are variable with normal to severe forms having lethargy, vomiting, hypotonia, seizures and coma. Anaemia, neutropenia, thrombocytopenia, hyperglycinaemia, hyperammonaemia and hypoglycaemia are common. Diagnosis can be confirmed by measuring propionate incorporation or mutase activity in cultured fibroblasts or by identifying the gene (*MUT* gene) mutation on chromosome 6p12.3 [68,70].

Tyrosinaemia

Three enzyme deficiencies cause tyrosinosis but only fumarylacetoacetate hydrolase (FAH) deficiency (type I) presents with hypoglycaemia. Fumarate in the tyrosine metabolic pathway is converted from fumaryl acetoacetate by FAH, deficiency results in accumulation of succinyl acetone in blood and urine (Figure 4). In the absence of fumarate, tyrosine does not enter the Krebs cycle and gluconeogenic pathway [71]. The elevated levels of succinyl acetone in serum and urine confirm the diagnosis. Tyrosinaemia type 1 is an AR trait. The gene for FAH has been mapped to choromosome15q, mutation resulting in tyrosinaemia [72].

Hereditary Defects in Fatty Acid Metabolism

Normal fatty acid metabolic pathway

Free fatty acids (FFA) are important substrates for ketogenesis to provide the brain with an "alternative fuel" source and for gluconeogenesis during the fasting state, especially after hepatic glycogen stores are depleted. During lipolysis, triglycerides are converted into fatty acids and glycerol. The FFAs in the blood stream are taken up by muscle and are converted to acyl-CoA by acyl-CoA synthetase. The process of β-oxidation converts the long carbon chains of FFAs to acetyl-CoA, which then enter the Krebs cycle. The "carnitine shuttle", catalysed by carnitine palmitoyltransferase-I and II (CPT- I and II), allows acyl-CoA to penetrate the outer and inner mitochondrial membranes respectively, facilitated by the inner membrane exchange transporter, carnitine-acylcarnitine translocase. Once inside the mitochondrial matrix, acetyl-coA is generated by β-oxidation of acyl-CoA via a 4-step process involving dehydrogenation, hydration, oxidation and thiolysis. Acetyl-CoA enters the Krebs cycle. The NADH and FADH2 produced by both fatty oxidation and in Krebs cycle are used by electron transport chain to produce ATP (Figure 2) [9].

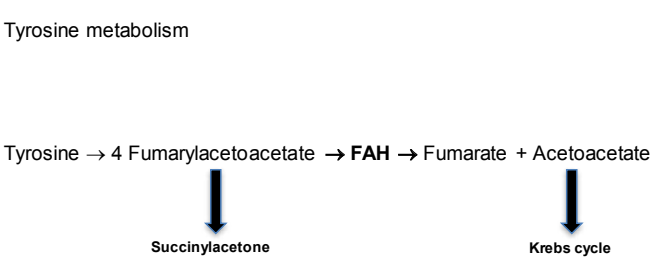

Figure 4: Outline of tyrosine metabolism. Fumarylacetoacetate formed in the process of tyrosine metabolism is broken down to fumarate and acetate by fumarylacetoacetate hydrolase (FAH). Acetoacetate, a ketone body, can be converted to acetyl-CoA, which in turn can enter Krebs cycle. Deficiency of FAH results in accumulation of succinyl acetone and causes the symptoms of Tyrosinaemia type 1.

Defects in β-oxidation causing hypoglycaemia

Medium-chain Acyl Co-A Dehydrogenase (MCAD) deficiency : The enzyme MCAD is responsible for the dehydrogenation step of fatty acids as they undergo β-oxidation to acetyl CoA in the mitochondria, providing energy after glucose and glycogen stores are exhausted [73] (Figure 2). Acetyl-Co A enters the Krebs cycle and when the capacity of Krebs cycle to metabolize acetyl-Co A exceeds so they are then converted to ketone bodies. In MCAD deficiency, the patient on prolonged fasting or illness develops hypoketotic hypoglycaemia. This usually presents in the first 3 years of life with vomiting, seizures and coma. Elevated ammonia levels, increased plasma $C_{8:0}$, $C_{10:0}$ and $C_{10:1}$ acylcarnitines and acylglycines are diagnostic markers [74]. MCAD is an AR inherited disorder. MCAD gene (*ACADM* gene) has been mapped on chromosome 1p31.1. Prenatal diagnosis can be made by demonstration of marked reduction in octanoate oxidation in cultured amniotic cells and enzyme assay of skin fibroblasts from the aborted foetus [75].

Long-chain 3-hydroxyacyl Co-A Dehydrogenase (LCHAD) deficiency: As in MCAD deficiency, LCHAD deficiency causes restriction of β-oxidation resulting in increased oxidation of glucose as a respiratory fuel to meet the demands for energy. If the reserves of glycogen are limited, this may result in severe hypoglycaemia. Clinical manifestations are severe hypoketotic hypoglycaemia and cardiomyopathy; typically appear for the first time after a fast. An elevated level of 3 hydroxy-acyl carnitine in blood spot or plasma is diagnostic [73]. LCHAD deficiency is an AR disorder with the gene (*HADHA* gene) located on chromosome 2p23.3. Prenatal diagnosis is possible by mutation analysis [76].

Short-chain 3-hydroxyacyl-CoA Dehydrogenase (SCHAD) deficiency: SCHAD deficiency is a rare fatty acid oxidation disorder presenting with hyperinsulinaemic hypoketotic hypoglycaemia. Most patients present with vomiting and seizures due to hypoglycaemia and unexpected deaths have been reported. SCHAD deficiency causes hyperinsulinism by activation of glutamate dehydrogenase (GDH) via loss of inhibitory regulation of GDH by SCHAD [77]. In some patients elevated levels of hydroxybutyryl-carnitine which might help with the diagnosis. Measurement of SCHAD activity in fibroblasts allows the diagnosis of affected individuals. SCHAD deficiency is an AR inherited disorder, caused by mutations in *HADH* gene located on chromosome 4q25 [78].

Disorders of Carnitine Metabolism

Primary carnitine deficiency

Primary carnitine deficiency is an AR disorder of fatty acid metabolism due to deficiency of functional organic cation transporters. Clinical features include lethargy, refusal of feeds, hepatomegaly, cardiomyopathy, hypotonia and rapid deterioration to coma and death. Biochemical analysis shows hypoketotic hypoglycaemia, hyperammonaemia and deranged liver function tests. Diagnosis is based on markedly reduced serum acylcarnitine and raised urinary carnitine levels [79]. Demonstrating reduced carnitine transport in skin fibroblasts from the patient confirms the diagnosis. Primary systemic carnitine deficiency is caused by mutations in the *SLC22A5* gene, which encodes the sodium ion-dependent organic cation\carnitine transporter (OCTN2), mapped on chromosome 5q31.1 [80].

Carnitine Palmitoyltransferase-I (CPT-I) deficiency

CPT-I deficiency presents with hepatic encephalopathy and severe hypoketotic hypoglycaemia precipitated by fasting or fever. Marked elevation of free carnitine level is characteristic of CPT-I deficiency [81]. The CPT-I enzyme defect can be demonstrated in cultured fibroblasts or lymphoblasts. Mutations in *CPT-I* gene lead to CPT-I deficiency and the gene is located on chromosome 11q13.3. Molecular genetic testing and biochemical analysis of cells obtained through chorionic villus biopsy or amniocentesis can facilitate prenatal diagnosis [82].

Carnitine-acylcarnitine Translocase – CACT deficiency

CACT is an inner mitochondrial membrane carrier protein for acylcarnitine, a deficiency of which will prevent the entry of long-chain fatty acids into the mitochondria for fatty acid oxidation. Patients usually present with fasting hypoglycaemia, hyperammonaemia and cardio respiratory collapse [79,83]. Diagnosis can be made using cultured fibroblasts or lymphoblasts. CACT deficiency is caused by mutations in the *SLC25A20* gene on chromosome 3p21.31 [83].

Carnitine palmitoyltransferase II (CPT-II) deficiency

Severe forms CPT-II deficiency leads to neonatal deaths with subtle dysmorphism, kidney and cerebral malformations. Lethal neonatal form and severe infantile form, both symptomatic with hypoketotic hypoglycaemia, hyperammonaemia may succumb to cardiorespiratory collapse. A late onset form presents with rhabdomyolysis, myoglobinuria and elevated creatinine kinase levels following exercise [81]. Demonstrating deficient enzyme activity in cultured fibroblast can make diagnosis. *CPT-II gene* is located on chromosome 1p32.3, mutation in which lead to CPT II deficiency. Molecular genetic testing using DNA obtained by amniocentesis or biochemical testing of amniocytes for CPT-II activity is diagnostic [84,85].

Disorders of Mitochondrial Metabolism

A large number of mitochondrial disorders can present with hypoglycaemia. Mitochondrial disorders usually present as a metabolic crisis in combination with one or several organ manifestations. Lactic acidosis, hypoglycaemia, elevated serum transaminases and conjugated bilirubin are common signs of mitochondrial hepatopathy. Mitochondrial depletion syndromes caused by mutations in *DGUOK, MPV17, SUCLG1, POLG1*, or *C10ORF2* have been identified that lead to mitochondrial hepatopathy [86]. In addition mutations in nuclear translation factor genes (*TRMU, EFG1*, and *EFTu*) of the respiratory chain enzyme complexes have recently been identified [86].

Disorders of Ketone Body Synthesis and Utilization

HMG-Co A synthase deficiency

HMG-Co A synthase is the rate-limiting step in the formation of ketones from acetyl-Co A in fatty acid beta-oxidation pathway [87]. This enzyme is expressed only in the liver. HMG-CoA synthase deficiency is an AR inherited disorder and presents with vomiting, lethargy, tachypnoea and dehydration to coma and possibly death. Hypoketotic hypoglycaemia is common. Hepatomegaly is seen with normal cardiac and skeletal muscle function [88]. The mutations in the gene for HMG-CoA synthase (*HMGCS2* gene) deficiency have been identified on chromosome 1p13-p12 [89].

HMG-Co A lyase deficiency

HMG-Co A lyase is a rate limiting enzyme that catalyses the conversion of HMG-CoA to acetoacetate. Patients with deficiency of HMG-Co A lyase enzyme become symptomatic in infancy or early childhood with vomiting, severe fasting hypoglycaemia, acidosis, dehydration and rapid deterioration into coma. Laboratory findings include acidosis mild ketosis and hyperammonaemia [87]. Diagnosis can be confirmed by enzyme assay in fibroblasts and leukocytes. This enzyme deficiency is AR inherited and the gene – *HMGCL* – has been mapped on chromosome 1p36.11. Prenatal diagnosis by assay of enzymes in cultured amniocytes is possible [90].

β-ketothiolase deficiency (Mitochondrial acetoacetyl CoA thiolase deficiency)

This enzyme deficiency causes a defect involving ketone body metabolism and isoleucine catabolism. Clinically β-ketothiolase deficiency is characterized by intermittent ketoacidotic crisis with normal interval periods. Clinical symptoms of ketoacidotic crisis include vomiting, dehydration, dyspnoea, hypotonia, lethargy, and convulsions and may progress to coma. Both hypo and hyperglycaemia and hyperammonaemia may be noted [91]. Diagnosis can be confirmed by assay of the enzyme in cultured fibroblasts. Mutations in *ACAT1* gene on chromosome 11q22.3 cause β-ketothiolase deficiency and are AR inherited [92].

Succinyl-CoA: 3-Ketoacid CoA Transferase –SCOT deficiency

SCOT deficiency is a ketolytic defect in which extra hepatic tissues cannot use the ketone bodies produced by the liver. Intermittent episodes of severe ketoacidosis on fasting with normal interval period are the characteristic feature of SCOT deficiency. Hypoglycaemia has been documented in these patients. Deaths have been reported following severe episodes of ketoacidosis. Deficient enzymatic activity can be shown cultured fibroblasts [93]. Genetic mutations have been identified on *SCOT* gene (OXCT1) on chromosome 5p13.1 in patients with this enzyme deficiency. Prenatal diagnosis can be made using amniocytes SCOT enzyme assay [94,95].

Syndromes Associated with Hypoglycaemia

Beckwith-wiedemann Syndrome (BWS)

Beckwith-wiedemann Syndrome (BWS) is a human loss-of-imprinting syndrome primarily characterized by macrosomia, macroglossia, abdominal wall defects and exhibits a predisposition to tumorigenesis. The relevant imprinted chromosomal region in BWS is 11p15.5, which consists of two imprinting domains, IGF2/H19 and CDKN1C/KCNQ1OT1 [96]. BWS has five known causative epigenetic and genetic alterations: loss of methylation (LOM) at KvDMR1, gain of methylation (GOM) at H19DMR, paternal uniparental disomy, CDKN1C mutations and chromosomal rearrangements [96]. BWS is the commonest syndrome associated with HH. Hypoglycaemia occurs in about 50% of children with BWS and, in the majority of infants, it resolves spontaneously. However, in a small group of patients the hypoglycaemia can be persistent and may require pancreatectomy. The mechanism of persistent HH in patients with BWS is unclear [97].

Laron syndrome

Laron syndrome (primary growth hormone resistance or insensitivity) is characterised by short stature associated with normal or high serum growth hormone (GH) and low serum insulin-like growth factor-1 (IGF1) levels, which fail to rise after exogenous GH administration. In the neonatal period they often present with hypoglycaemia and micropenis. Hypoglycaemia is common in the

infancy and childhood periods. Clinical features include protruding and high forehead, shallow orbits, hypoplastic nasal bridge and small chin. They have relative obesity and the puberty is often delayed. Laron syndrome is due to mutations in the *GHR* gene (5p13-p12), resulting in low growth hormone binding protein levels and defective IGF-I production. Transmission is AR. A Laron syndrome-like phenotype with associated with immunodeficiency is due to gene dysfunction of the signal transducer and activator of transcription 5b (STAT5b). Mutations in *STAT5b* have also been observed in typical Laron syndrome [98].

Primary Generalised Glucocorticoid Resistance (PGGR)

PGGR causes a glucocorticoid action defect, characterised by activation of the hypothalamic-pituitary-adrenal (HPA) axis, elevated levels of corticotropin-releasing hormone and adrenocorticotropic hormone and high levels of adrenal cortical hormones. Chronic fatigue is the presenting feature in some patients and profound hypoglycaemia has been reported in those with complete glucocorticoid resistance. Clinical manifestations of mineralocorticoid excess (hypertension, hypokalaemic alkalosis) and androgen excess (ambiguous genitalia, gonadotropin-independent precocious puberty) are often seen. PGGR is primarily due to mutations in the *hGR* (human glucocorticoid receptor) gene, located on the long arm of chromosome 5 (q31.3). The molecular mechanisms through which these *hGR* mutants affect glucocorticoid signal transduction have been identified in reported cases of glucocorticoid resistance [99].

Extreme insulin resistance syndromes

Leprechaunism and Rabson-Mendenhall Syndrome are extreme insulin resistance syndromes that are associated with hypoglycaemia. They are AR inherited disorders due to mutations in the insulin receptor gene (*INSR*; 19p13.3-p13.2) [100].

Leprechaunism is the most severe form of insulin resistance; characterized by severe growth retardation, dysmorphism, lipatrophy and muscular hypotrophy. These patients experience episodes of hypoglycaemia due to an accelerated fasting state secondary to insulin resistance [101,102].

Rabson-Mendenhall syndrome is a rare disorder characterized by growth retardation, dysmorphism, enlarged genitalia, hypertrichosis, coarse facies, fasting hypoglycaemia, postprandial hyperglycaemia and extreme hyperinsulinaemia [103].

Soto's syndrome

Soto's syndrome is characterised by a typical facial appearance, overgrowth and learning disability that may be mild to severe. Neonatal hypoglycaemia has been reported in 2-15% of Soto's syndrome cases. Soto's syndrome is caused by heterozygous mutation in the NSD1 gene or by a deletion in the 5q35 region including genomic sequence in addition to the *NSD1* gene [104].

Timothy syndrome

Timothy syndrome is a calcium channelopathy characterised by cardiac, hand, facial and autism caused by mutations in the CaV1.2 L-type calcium channel gene, *CACNA1C* mapped on 12p13.33. These patients suffer from intermittent hypoglycaemia (HH) and death usually follows severe ventricular tachyarrythmia [105].

Miscellaneous Disorders

Defects in citrin metabolism

Citrin is the hepatic mitochondrial aspartate glutamate carrier. Citrin deficiency is an AR genetic disorder causing metabolic derangements in aerobic glycolysis and gluconeogenesis. The citrin protein transports aspartate from mitochondria to cytoplasm which is essential for converting citrulline to arginosuccinic acid. Therefore, deficiency of citrin disrupts the urea cycle. Clinical manifestations include neonatal intrahepatic cholestasis (NICCD), failure to thrive and dyslipidaemia due to citrin deficiency (FTTDCD) and recurrent hyperammonaemia [106,107]. Hypoglycaemia is consistent in both NICCD and FTTDCD. A diagnosis of citrin deficiency can be made with the elevated plasma levels of ammonia, citrulline and arginine. A biallelic mutation in *SLC25A12* gene on chromosome 7q21.3 confirms the diagnosis [108].

AKT2 mutations causing hypoglycaemia

AKT (Protein Kinase B) plays a key role in multiple cellular processes such as glucose, lipid and amino acid metabolism, cell division and apoptosis. AKT2 is more specific for the insulin receptor-signalling pathway and activation of AKT2 mediates the effects of insulin on body tissues. Gain-of-function AKT2 mutations result in severe hypoglycaemia by inhibiting hepatic glucose production. These patients have severe fasting hypoglycaemia requiring continuous gastric feeding to maintain normal plasma glucose levels. Their biochemical picture resembles hyperinsulinaemic hypoglycaemia (hypoketonaemia, low serum fatty acids and low levels of branched chain amino acids) except for undetectable plasma insulin levels. The mutation leads to glutamate-to-lysine substitution at position 17 in the pleckstrin homology domain of AKT2 and results in constitutive plasma membrane localization and activated signalling. *AKT2* gene has been mapped on chromosome 19q13.1-q13.2 causing hypoinsulinaemic hypoglycaemia with hemi-hypertrophy (HIHGHH) [109,110].

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