

What's new in metabolic and genetic hypoglycaemias: diagnosis and management

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Abstract Hypoglycaemia in children can be a life-threatening situation that needs to be assessed rigorously in order to treat efficiently and avoid relapse that can be responsible for cerebral damage. The diagnosis of impairment in glucose homeostasis requires the knowledge of the mechanisms regulating blood glucose concentration. The clinical history and presentation, when available, especially the timing of hypoglycaemia with respect to the last meal and some simple clinical and biological tests may allow diagnosing the vast majority of patients presenting with hypoglycaemia. Recently,

new metabolic and endocrinologic genetic causes of hypoglycaemia have been identified that may give new insight to the complex mechanisms of glucose regulation and thus contribute to the discovery of new genes regulating glucose homeostasis. New diagnostic tests such as the 18-fluoro-Dopa PET-scan have also been recently developed.

Keywords Hypoglycaemia · Hyperinsulinism · Metabolic · Diagnosis · Children

Abbreviations

| | |
|--------|--|
| ATP: | Adenosine triphosphate |
| BWS: | Beckwith-Wiedemann syndrome |
| CDG: | Congenital disorders of glycosylation |
| FAO: | Fatty acid oxidation |
| FBS: | Fanconi-Bickel syndrome |
| GDH: | Glutamate dehydrogenase |
| GH: | Growth hormone |
| GK: | Glucokinase |
| GTP: | Guanosine triphosphate |
| HI: | Hyperinsulinism |
| HIHA: | Hyperinsulinism-hyperammonemia syndrome |
| IGF1: | Insuline-like growth factor 1 |
| MCT: | Mean chain triglycerides |
| PET: | Positron emission tomography |
| SCHAD: | Short chain 3-hydroxyacyl-CoA dehydrogenase deficiency |
| TBG: | Thyroxin-binding globulin |

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Introduction

Hypoglycaemia, defined by a glucose plasma level below 3 mmol/l (55 mg/dl) in children and below 2 mmol/l (1st

24 h of life) to 2.5 mmol/l (35–45 mg/dl) in neonates, can be a life-threatening situation that needs to be assessed rigorously in order to treat efficiently and avoid relapse that can be responsible for cerebral damage [17]. Hypoglycaemia results from an impairment of glucose homeostasis and the diagnosis of its causes requires a good knowledge of the complex mechanisms which maintain blood glucose concentration between the narrow range of 2.5 and 6.6 mmol/l at the fasting or fed state [5]. The clinical history and presentation, when available, may allow diagnosing the cause of hypoglycaemias in more than 90% of patients.

The main clinical criteria for diagnosis are the timing of hypoglycaemia with respect to the last meal and the presence or absence of an enlarged liver (Fig. 1). Associated symptoms, like responsiveness to glucagon administration, vomiting, bleeding, or a multi-organ failure may also be essential to orientate diagnosis. Simple biochemical data such as blood lactate and blood and urine ketone bodies, easily measured in urine using a ketone-detecting dipstick, are also important diagnostic clues, especially in

fasting hypoglycaemias. During feeding, the liver builds up energy stores in the form of glycogen and triglycerides, the latter being exported to adipose tissue. Conversely, during fasting, it releases glucose and ketone bodies. The maintenance of a normal blood glucose level depends upon: (1) hepatic glycogenolytic and gluconeogenic enzymes, (2) an adequate supply of endogenous gluconeogenic substrates (amino acids, glycerol, and lactate), (3) an adequate energy supply provided by β -oxidation of fatty acids needed to synthesize glucose and ketone bodies, the latter being exported to peripheral tissues and preferentially used as an alternative fuel to glucose, and (4) a normal endocrine system for integrating and modulating these processes. The major signals, which control the transition between the fed (postprandial) and the fasting states, are glucose, insulin, and glucagon blood levels [29, 30, 41]. Based on the origin of the glucose in blood, it is possible to divide glucose homeostasis time course into five phases. The timing of hypoglycaemia with respect to the last meal is a valuable diagnostic element. The diagnostic algorithm

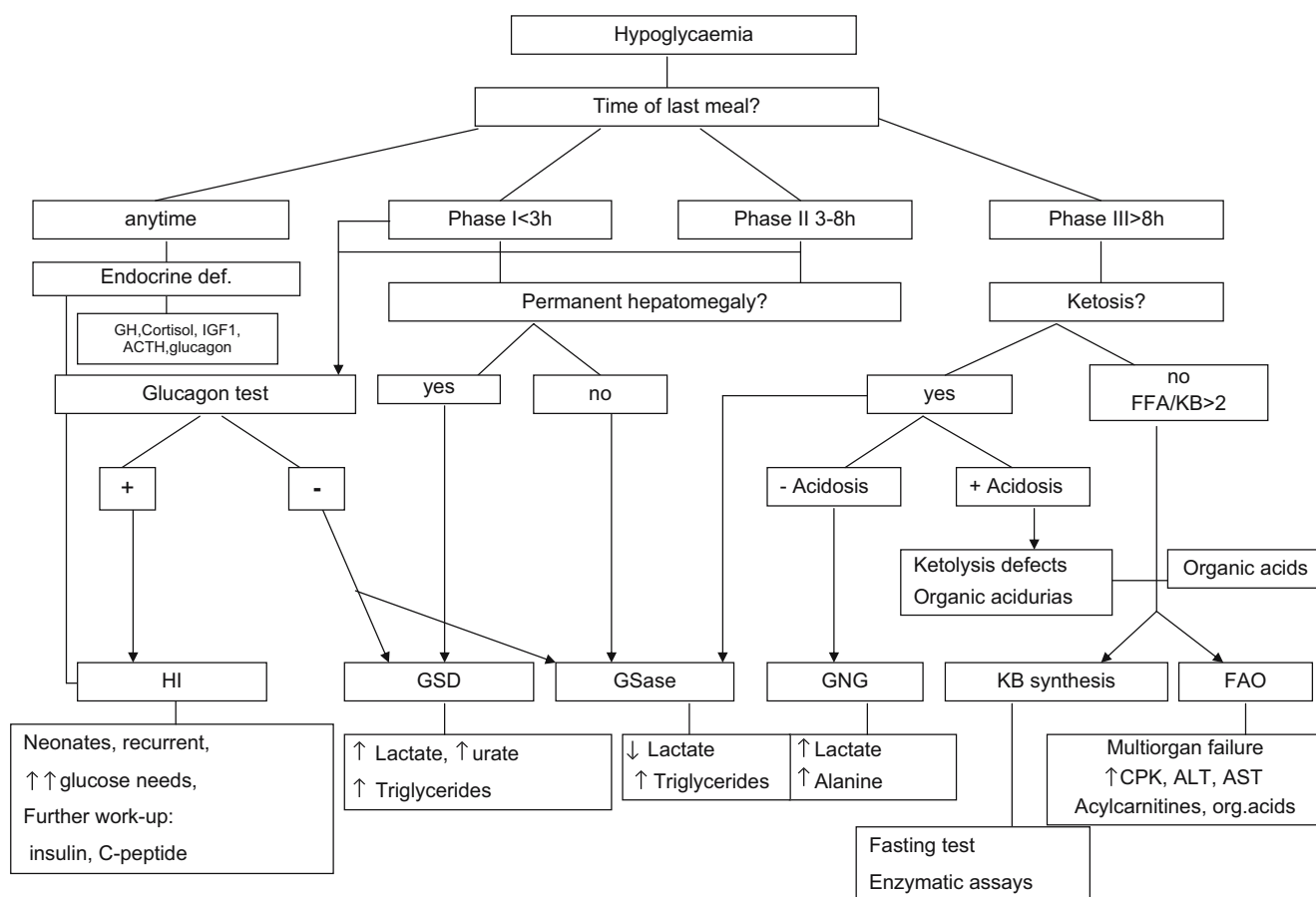


Fig. 1 Diagnostic algorithm for hypoglycaemia. Timing of hypoglycaemia is the main diagnostic criterion. Simple clinical and biochemical signs such as hepatomegaly, acidosis, ketosis, lactate, and triglycerides are crucial diagnostic elements. *HI* hyperinsulinism, *GSD* glycogen storage disorders, *GSase* glycogen synthase deficiency, *GNG* gluconeogenesis defects, *KB*

synthesis ketone bodies synthesis defects, *FAO* fatty acid oxidation defects, *KB* ketone bodies, *FFA* free fatty acids, *GH* growth hormone, *IGF1* insulin growth factor-1, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase

is presented in Fig. 1. The glucagon test is a useful diagnostic test for short-fasting hypoglycaemia (<8 hours of fasting). It is considered as “positive” when blood glucose levels double within the first 15 minutes following the injection of 1mg of glucagon parenterally. Hereditary intolerance of galactose and fructose are two rare causes of postprandial hypoglycaemia that are not displayed in Fig. 1 and are always associated with specific digestive signs (vomiting) and liver dysfunction.

The essential, nonspecific emergency treatment of hypoglycaemia is to administer glucose either orally if the child is conscious or through a nasogastric tube. Oral administration of 10 or 20 ml of a 30% glucose solution is in most cases sufficient to raise glucose levels to normal values. When the cause is not identified it may be reasonable to pursue glucose administration continuously either through a nasogastric tube or IV line. The glucose rate that has to be administered must be at least equal at the maximum liver output of glucose from glycogen (8–10 mg/kg/mn of glucose for a neonate or young infant, 6–7 mg/kg/mn for children). Hypoglycaemia can be easily controlled in all cases by these rates of intravenous glucose except in severe hyperinsulinism (HI) where it may be insufficient, and continuous glucagon infusion (0.5–2 mg/day) along with glucose should be administered. Specific treatments

should be given as soon as the final diagnosis is strongly suspected or established (Table 1).

Recently, new causes of hypoglycaemia such as glucose transporter disorders, respiratory chain disorders and congenital disorders of glycosylation have been identified. In addition, new genes and syndromes have been reported in hyperinsulinism (HI), which can be considered as the mirror of diabetes. The management of the latter has been improved by the use of a new diagnostic tool, [18F]fluoro-DOPA PET-scan [9]. In this paper we will focus on new genetic causes of hypoglycaemia that give insight into the complex regulatory mechanism of blood glucose.

Congenital hyperinsulinism and genetic syndromes associated with hyperinsulinism and hypoglycaemia

Hyperinsulinism is a heterogeneous disorder of primary origin or in rare cases secondary to other defects. In the latter, hypoglycaemia is not isolated. The diagnostic criteria for congenital hyperinsulinism (HI) are given in Table 1. In the neonatal period diagnosis is often easy, mostly based on the severity of hypoglycaemia occurring within 72 hours after birth and the glucagon responsiveness. The majority of newborns display macrosomy at birth. Hypoglycaemia is

Table 1 Diagnostic clues, confirmation tests, and specific treatment for the most frequent genetic causes of hypoglycaemia

| Disease | Clues to diagnosis | Diagnostic tests | Specific treatment |
|---|--|--|--|
| Hyperinsulinism | Pre and postprandial hypoglycaemia, positive glucagon response inappropriately high insulin levels for plasma glucose <2.7 mmol/l (50 mg/dl) | Molecular screening SUR1/Kir 6.1 / other genes [18F] fluoro-DOPA PET scan | Diazoxide, somatostatin, calcium channel blockers, pancreatic surgery |
| Fatty acid oxidation disorders | Fasting hypoketotic (free fatty acids/ ketone bodies>2 mmol/l) hypoglycaemia, multi-organ failure, abnormal organic acids, acylcarnitins | Overall FAO and specific enzymatic assays and molecular diagnosis | Prevent fasting and lipolysis by dietary treatment, MCT in long chain FAO disorders, L-Carnitine |
| Glycogen storage disorders | Short fasting hypoglycaemia, permanent hepatomegaly, negative glucagon response, high lactate (when gluconeogenesis also impaired), high triglycerides and uric acid | Enzymatic and molecular studies | Dietary treatment: raw cornstarch between meals, continuous night feeding |
| Neoglucogenesis disorders | Fasting hypoglycaemia, hepatomegaly during hypoglycaemia, high lactate and alanine | Enzymatic and molecular studies | Prevent prolonged fasting and catabolic states |
| Ketone bodies synthesis | Fasting hypoketotic hypoglycaemia | Enzymatic and molecular studies | Prevent prolonged fasting and catabolic states |
| Ketolysis defects and organic acidurias | Fasting hypoglycaemia, severe ketoacidosis, coma | Enzymatic and molecular studies | Prevent prolonged fasting and catabolic states |
| Hormonal deficiencies | No specific timing, micropallus, growth failure | Function tests, molecular studies | Recombinant hormone treatment |

always severe, revealed by seizures in many cases, with risk of brain damage [10, 17]. The rates of administered glucose required to prevent hypoglycaemia are elevated to values close to 17 mg/kg/mn in our series. Most often, no other symptoms are associated with hypoglycaemia. Facial dysmorphism with high forehead, large and bulbous nose with short columella, smooth philtrum and thin upper lip is frequently observed in all types of hyperinsulinism [7].

Hyperinsulinemic hypoglycaemia is due to an inappropriate insulin secretion by the β cells of Langerhans islets. Insulin is the only hormone to lower glucose concentration in plasma. It does it by both inhibiting glucose release from hepatic glycogen and by increasing glucose uptake in muscle cells. This explains the two main characteristic clinical findings of neonatal HI: the high glucose requirement to correct hypoglycaemia and the responsiveness of hypoglycaemia to exogenous glucagon. Several pathways are involved in the regulation of insulin secretion by the

pancreatic β -cell, and this helps to explain the effectiveness of the different medical treatments, such as oral diazoxide (5–15 mg/kg/day), somatostatin injections (10–50 μ g/day in three injections or continuous infusion), calcium channel inhibitors (nifedipine 0.5–2 mg/kg/d), and a protein (leucine) restricted diet (Fig. 2) [23, 24].

Patients who are resistant to medical treatment and require surgical treatment have to be classified according to histological criteria [32]. A focal form is defined as a focal adenomatous hyperplasia. In the diffuse HI, histological abnormalities involve the whole pancreas [11]. In the absence of any distinctive clinical feature, a pancreatic venous catheterization and sampling of glucose, insulin, and C-peptide [11] and pancreatic arteriography were until recently the only preoperative procedures available for locating the site of insulin secretion. Recently an 18-fluoro-DOPA PET-scan has shown efficacy in distinguishing focal from diffuse forms. Pancreatic β -cells are neuroendocrine

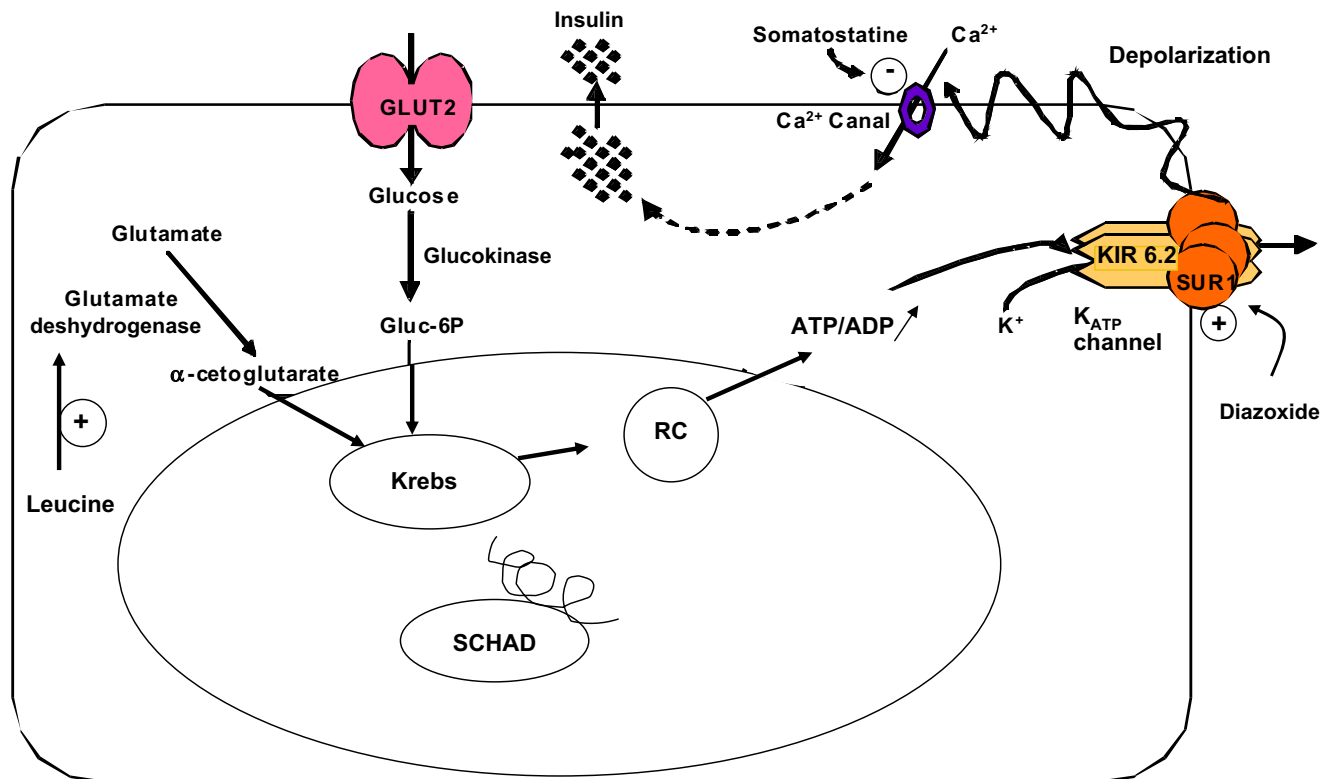


Fig. 2 Schematic representation of the regulation of insulin secretion by the pancreatic β -cell. GLUT2 catalyses glucose uptake by β -cells. Glucokinase, the enzyme that initiates β -cell glucose metabolism, has a high K_m for glucose, and thus the circulating concentrations of glucose directly determine the rate of glucose oxidation and subsequent release of insulin. Glucose and leucine, a potent positive allosteric effector of glutamate dehydrogenase (GDH), interact with the Krebs cycle activity resulting in ATP synthesis. This results in an increase of the intracellular ratio of the ATP/ADP ratio that activates a plasma membrane protein, the sulfonylurea receptor (SUR1), to cause the closure of the potassium channel (K_{ATP}), leading to depolarization of the cell membrane, influx

of extracellular calcium, and release of insulin from storage granules. An increased GDH activity resulting from mutations of the GDH gene (dominant positive effect) is responsible for increased α -ketoglutarate levels and consecutively increased Krebs cycle activity and β -cell ATP/ADP ratio and, subsequently, an exaggerated insulin release. These regulation mechanisms account for the efficacy of medical treatments such as diazoxide, somatostatin, and in a protein (leucine) restricted diet on insulin secretion. GLUT2 glucose transporter, G6P glucose-6-phosphate, α -KG α -ketoglutarate, Krebs Krebs cycle, RC mitochondrial respiratory chain, KIR 6.2 inward-rectifying potassium channel, SCHAD short-chain 3-hydroxyacyl-CoA dehydrogenase

cells and can take up [18F]fluoro-L-dopa converted into dopamine by DOPA decarboxylase. A good correlation between the localization of DOPA decarboxylase and proinsulin in normal pancreas and in both diffuse and focal HI tissues has been demonstrated by immunochemistry studies on pancreatic surgical samples [9].

The most common mechanism underlying HI is dysfunction of the pancreatic ATP-sensitive potassium channel (K_{ATP}^+). The two subunits of the K_{ATP}^+ channel are encoded by the sulfonylurea receptor gene (*SUR1* or *ABCC8*) and the inward-rectifying potassium channel gene (*KIR6.2* or *KCNJ11*), both located in the 11p15.1 region. HI ‘channelopathies’ are due to inhibiting *SUR1* or *KIR6.2* mutations. These mutations can lead to type 1 channelopathy without channel activity, or to type 2 channelopathy with a decreased channel activity due either to defective function, or to decreased number of channels. Heterogeneous outcome is observed for the same mutation as some cells manifest a type 1 channelopathy, others a type 2 channelopathy, and other mutated cells have a normal activity of the potassium channel [6, 39]. This observation could be explained by interactions with modulator genes, exogenous factors, or variable degree of penetrance of the mutation.

Mutations of the *SUR1* gene are responsible for 50–60% of HI, either focal or diffuse HI, especially in neonates. More than 100 distinct mutations, distributed throughout the *SUR1* gene, have already been described. Mutations of the *KIR6.2* gene are less frequent and are responsible for 10–15% of HI [12, 13].

The histopathological lesions associated with neonatal HI may be described as diffuse or focal. Focal adenomatous islet cell hyperplasia is sporadic and has been demonstrated to arise in individuals who have a germline mutation in the paternal allele of the sulfonylurea-receptor *SUR1* gene or the inward-rectifying potassium-channel *Kir6.2* in addition to a somatic loss of the maternally derived chromosome region 11p15 in adenomatous pancreatic beta-cells. Diffuse HI may be familial and arises from the autosomal recessive inheritance of mutations in both the *SUR1* and *Kir 6.2* genes. The therapeutic outcome for patients is heavily dependent upon distinguishing between the two histopathological lesions. Diffuse HI, which are unresponsive to medical treatment, require extensive pancreatectomy with a high risk of diabetes. Conversely, focal HI can be cured by limited pancreatectomy. Genetic counseling is dramatically different as focal HI is considered a sporadic molecular event with a very low recurrence risk, while diffuse HI is inherited in a recessive pattern for neonatal onset forms and dominant or sporadic transmission for late onset HI [40].

Hyperinsulinism may also be due to metabolic causes where increase of the ATP/ADP ratio in pancreatic β -cells

is responsible for inappropriate insulin secretion (Fig. 2). In the cases which follow, the K_{ATP}^+ channels are functional, explaining the fact that hypoglycaemia responds to treatment by diazoxide.

Dominantly expressed glucokinase (GK) mutations

Dominantly expressed glucokinase (GK) mutations are a rare cause of HI [14]. They result in a gain of function by increased affinity of GK for glucose leading to inappropriate insulin secretion. These mutations are remote from the glucose-binding site and suggest an allosteric regulation defect.

Hyperinsulinism-hyperammonemia syndrome (HIHA)

The second most common form of congenital hyperinsulinism, the hyperinsulinism/hyperammonemia syndrome (HIHA), is associated with dominantly expressed missense mutations of the mitochondrial enzyme, glutamate dehydrogenase (GDH). GDH catalyzes the oxidative deamination of glutamate to alpha-ketoglutarate plus ammonia. HIHA mutations impair GDH sensitivity to its allosteric inhibitor, GTP, resulting in a gain of enzyme function and increased sensitivity to its allosteric activator, leucine. The phenotype is dominated by hypoglycaemia, usually postprandial, following high-protein meals, as well as fasting hypoglycaemia. Plasma ammonia levels are increased 3–5 times normal due to expression of mutant GDH in liver, probably reflecting increased ammonia release from glutamate as well as impaired synthesis of N-acetyl glutamate, due to reduction of hepatic glutamate pools. Ammonia levels are unaffected by feeding or fasting [38]. However, some patients present epilepsy and mental retardation that may be related to effects of GDH mutations in the brain, perhaps in combination with effects of recurrent hypoglycaemia and chronic hyperammonemia [33].

Short chain 3-hydroxyacyl-CoA dehydrogenase deficiency (SCHAD)

A few hyperinsulinemic patients have been reported to have a mutation in the gene encoding short-chain 3-hydroxyacyl-CoA dehydrogenase (SCHAD), an enzyme participating in mitochondrial fatty acid oxidation. The patients present with neonatal severe hyperinsulinism, enhanced levels of 3-hydroxybutyryl-carnitine in their blood plasma, and greatly reduced SCHAD activity in fibroblasts. Urine metabolite analysis showed that SCHAD deficiency resulted in specific excretion of 3-hydroxyglutaric acid [26]. Recent reports suggest that mitochondrial fatty acid oxidation influences insulin secretion through a K_{ATP}^+ channel-independent mechanism [16].

Exercise-induced hyperinsulinism

Exercise-induced hyperinsulinism is a novel, autosomal dominant form of HI, which has been identified in two families. The patients suffer from hypoglycaemic symptoms only when performing strenuous physical exercise [28]. The underlying mechanism of hypoglycaemia is unclear, but probably linked to anaerobic glycolysis as pyruvate administration leads to increased insulin secretion and hypoglycaemia and seems to be a reliable diagnostic test of this condition.

Many other genes could also be involved in HI, particularly those playing a role in insulin secretion, as recently described with *HNF4A* mutations in maturity-onset diabetes (MODY) and HI [31], and mutations of the insulin receptor (*INSR*) gene that was recently implicated in a dominant form of hyperinsulinemic hypoglycaemia [20]. Patients presented with postprandial as well as fasting hyperinsulinemic hypoglycaemia associated with resistance to insulin. Mutations in the gene encoding pro-hormone convertase-1 leading to abnormal or absent proinsulin processing are also responsible for hyperinsulinemic-like hypoglycaemia associated with diarrhoea and obesity [22].

Finally, hyperinsulinemic hypoglycaemia can be ‘syndromic’ as observed in the following overlapping syndromes.

Overgrowth syndromes with diazoxide sensitive hypoglycaemia

Beckwith-Wiedemann syndrome (BWS)

Should be looked for when exomphalos, macroglossia, or gigantism including length are noted, because the patients have an increased risk of developing specific tumors [4]. BWS results from several identified genetic and epigenetic molecular events including paternal isodisomy, abnormal methylation of *IGF2/H19*, chromosomal aberrations involving the 11p15 region, and *CDKN1C* mutation. Hypoglycaemia in BWS patients has been associated with paternal uniparental disomy of 11p15 rather than other genetic abnormalities, but the pathophysiological mechanism leading to hyperinsulinic hypoglycaemia is still unclear as no evidence for duplication of *INS*, *HRAS1*, and *IGF2* or overexpression of the *INS* and *IGF2* genes was found [19, 37].

Simpson-Golabi-Behmel syndrome (SGBS)

Simpson-Golabi-Behmel syndrome is an X-linked condition that shows phenotypic similarities to Beckwith-Wiedemann syndrome. Shared clinical features of BWS and SGBS include macrosomia, macroglossia, cleft palate,

visceromegaly, earlobe creases, hernias, neonatal hypoglycaemia, and a risk of embryonal tumors [21].

Perlman syndrome and Sotos syndrome

Perlman syndrome and Sotos syndrome are two overgrowth syndromes that have been associated with congenital hyperinsulinism [1, 18]. The mechanisms of hypoglycaemia in syndromic HI with gigantism remain unclear. Hyperplasia of β -cells, due to the overexpression of *IGF2* and/or an imbalance between *IGF2* and tumor suppressor genes (*H19*, *P57*), has been suggested. In Sotos syndrome a majority of patients displayed mutations on the *NSD1* gene that could be involved in imprinting of the 11p15 region [1].

Usher syndrome type 1C

Usher syndrome type 1 describes the association of profound, congenital sensorineural deafness, vestibular hypofunction and childhood onset retinitis pigmentosa. It is an autosomal recessive condition and is subdivided on the basis of linkage analysis into types 1A through 1E. Usher type 1C maps to the region containing the genes *ABCC8* and *KCNJ11* (encoding components of ATP-sensitive K⁺ (KATP) channels), which may be deleted in patients who present with hyperinsulinism [2].

Kabuki syndrome (KS)

Kabuki syndrome is a rare multiple congenital syndrome with an estimated frequency of 1/32,000 in Japan. Five major criteria delineate KS, namely, postnatal short stature, skeletal anomalies, moderate mental retardation, dermatoglyphic anomalies, and a characteristic facial dysmorphism. Some rare and atypical features have been reported including chronic and/or severe diarrhea, diaphragmatic defects, pseudarthrosis of the clavicles, vitiligo, and persistent hypoglycaemia. Hypoglycaemia in KS, which can be underestimated, may be due to HI or to growth hormone deficiency. The molecular basis of KS remains unknown.

Congenital disorders of glycosylation (CDG)

Congenital disorders of glycosylation (CDG) are genetic defects in the assembly of the carbohydrate moiety of glycoconjugates. This results in abnormal structure and function of proteins in many organs. The clinical spectrum of the disease in children is heterogeneous. Phosphomannose-mutase deficiency (CDG type 1a) is a multisystemic disease with dysmorphic features (abnormal fat distribution and inverted nipples), significant neurologic involvement (hypotonia, hyporeflexia, ataxia, convulsions, and psycho-

motor retardation), and failure to thrive. Other features are cerebellar hypoplasia, hypothyroidism, thyroxin-binding globulin (TBG) deficiency, strabismus, retinitis pigmentosa, vomiting, feeding difficulties, hepatomegaly, liver fibrosis, elevated transaminase concentration, coagulopathy, and hypoalbuminemia. Children may have cardiomyopathy, pericardial effusion, protein-losing enteropathy, or lymphoedema. In phosphomannose-isomerase deficiency (CDG type Ib), neurologic symptoms are usually absent. Clinical presentations are hypoglycaemia, hypothyroidism, TBG deficiency, vomiting, feeding difficulties, diarrhea, failure to thrive, protein-losing enteropathy, hepatomegaly, elevated transaminase concentration, congenital hepatic liver fibrosis, and coagulopathy. Children with CDG type Ia and those with type Ib may have hyperinsulinaemia and hypoglycaemia, occurring most frequently during episodes of gastroenteritis [3, 8]. Children with CDG type Ib should be treated with mannose. Patients with CDG type I can be identified by isoelectric focusing of serum transferrin, enzyme analysis, and/or DNA analysis.

Metabolic causes of hypoglycaemia not associated with hyperinsulinism

Glucose transporter deficiencies

Here is the place to recall the fascinating story of the Fanconi Bickel syndrome (FBS), the pathophysiology of which was recently identified [34, 35]. FBS is a rare well-defined clinical entity, inherited in an autosomal recessive mode. It is characterized by hepato-renal glycogen accumulation. Fasting hypoglycaemia, as well as postprandial hyperglycaemia and hypergalactosaemia, indicate an impaired utilization of these two monosaccharides, and a proximal renal tubular dysfunction. In contrast to other types of glycogen storage diseases caused by enzymatic defects of glycogenolysis, FBS has recently been shown to result from a defective monosaccharide transporter, GLUT2, in cell membranes of different tissues. It thus represents the first disease with hypoglycaemia caused by a defect of a member of the facilitative glucose transporter family. The diagnosis of this disorder, easily suspected on the very suggestive clinical pattern, relies upon the molecular investigation of the GLUT2 gene [34]. Defects in GLUT1 activity, another glucose transporter, is responsible for infantile seizures, acquired microcephaly, and developmental delay [36], but not hypoglycaemia. This deficiency results in reduced cerebrospinal fluid glucose concentrations (hypoglycorrhachia) and reduced erythrocyte glucose transporter activities in patients. The appropriate diagnosis is important as a ketogenic diet can improve symptoms.

Respiratory chain deficiency

We recently described two patients affected with respiratory chain deficiency (complex III and complex IV deficiency) who presented with isolated recurrent attacks of fasting hypoglycaemia [25]. During a fasting test, the first patient showed evidence for impaired gluconeogenesis (progressive increase of plasma lactate and no decrease of alanine levels), whereas the second patient appeared to have impaired fatty acid oxidation (hypoketotic hypoglycaemia with increased levels of nonesterified fatty acids). In both cases lack of ATP has been suggested to be responsible for secondary deficiency of ATP-dependant enzymes of gluconeogenesis.

Citrin deficiency

A deficiency of citrin, which is encoded by the SLC25A13 gene, causes both adult-onset type II citrullinaemia (CTLN2) and neonatal intrahepatic cholestasis (NICCD). The clinical features of the disease in neonates and infants include mainly severe intrahepatic cholestasis with fatty liver and variable accompanying clinical features, namely, failure to thrive, hemolytic anemia, bleeding tendencies, and ketotic hypoglycaemia. Laboratory data show elevated serum bile acid levels, hypoproteinaemia, low levels of vitamin K-dependent coagulation factors, and hypergalactosaemia. Hypercitrullinaemia is detected in most patients. Most of the reported patients were given a lactose-free and/or medium chain triglycerides-enriched formula and lipid-soluble vitamins. Symptoms resolved in most patients by 12 months of age. However, a few patients suffered from progressive liver failure and underwent liver transplantation before their first birthday. Another patient developed citrullinaemia type II (CTLN2) at the age of 16 years [15, 27].

Conclusions and research directions

In our experience, most of the genetic causes of hypoglycaemia are rather easy to elucidate. The diagnosis relies upon a limited number of parameters, mostly clinical and some simple biological tests. Careful history-taking and research for specific clinical features are very important (age at onset, severity and frequency of hypoglycaemic attacks, timing of hypoglycaemia, glucose requirement to maintain normal blood glucose concentrations, ketosis, glucagon responsiveness, hepatomegaly, short stature, dysmorphic features, etc.). The knowledge of the homeostatic mechanisms, which maintain blood glucose in early life is crucial to the diagnosis. It is also extremely important to collect appropriate blood and urine samples at the time of the acute event that most of the time will orientate the diagnosis. Symptomatic treatment is simple but urgent and

specific treatment should be started as soon as definitive diagnosis is suspected or established. New genetic syndromes have been discovered, most of them associated with hyperinsulinic hypoglycaemia, and new genes will probably be discovered implicated in hypoglycaemia, namely, all genes playing a role in glucose regulation.

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