9 Disorders of Fructose Metabolism

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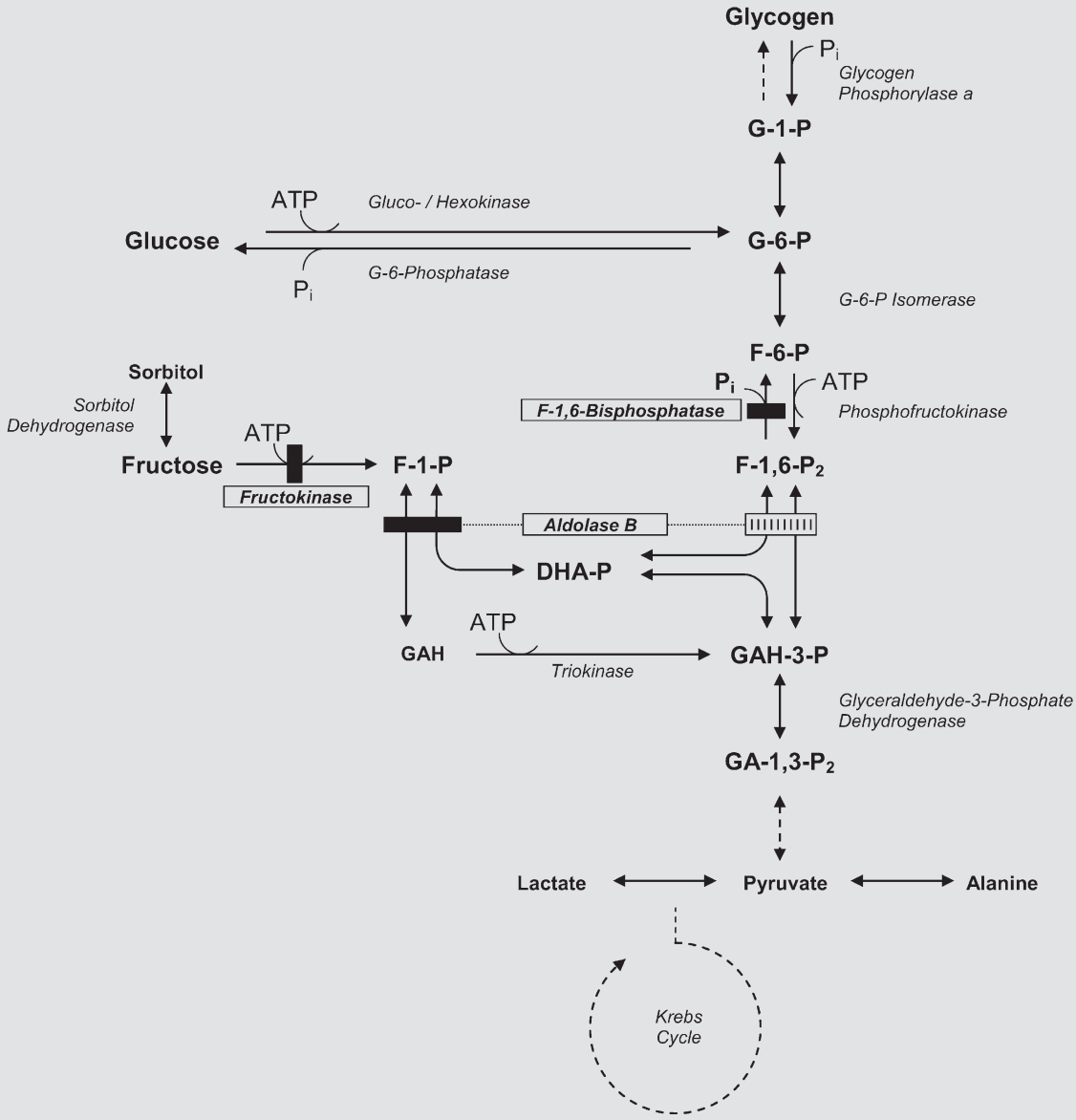
II

Fructose Metabolism

Fructose is one of the main sweetening agents in the human diet. It is found in its free form in honey, fruits and many vegetables, and is associated with glucose in the disaccharide sucrose in numerous foods and beverages. Sorbitol, also widely distributed in fruits and vegetables, is converted into fructose in the liver by sorbitol dehydrogenase (◘ Fig. 9.1). Fructose is mainly metabolized in the liver, renal cortex and small intestinal mucosa in a pathway composed of fructokinase, aldolase B and triokinase. Aldolase B also intervenes in the glycolytic-gluconeogenic pathway (right hand part of the scheme).



◘ **Fig. 9.1.** Fructose Metabolism. *DHA-P*, dihydroxyacetone phosphate; *F*, fructose; *G*, glucose; *GA*, glycerate; *GAH*, glyceraldehyde; *P*, phosphate; *Pi*, inorganic phosphate. The three enzyme defects in fructose metabolism are boxed and depicted by *solid bars* across the *arrows*; the diminished activity of aldolase B toward fructose-1,6-bisphosphate in hereditary fructose intolerance is depicted by a *broken bar*

Three inborn errors are known in the pathway of fructose metabolism depicted in ◘ Fig. 9.1. *Essential fructosuria* is a harmless anomaly characterized by the appearance of fructose in the urine after the intake of fructose-containing food. In *hereditary fructose intolerance* (HFI), fructose may provoke prompt gastrointestinal discomfort and hypoglycemia upon ingestion, symptoms that may vary from patient to patient and depend on the ingested dose. Fructose may cause liver and kidney failure when taken persistently, and its intake becomes life-threatening when given intravenously. *Fructose-1,6-bisphosphatase* (FBPase) *deficiency* is also usually considered an inborn error of fructose metabolism although, strictly speaking, it is a defect of gluconeogenesis. The disorder is manifested by the appearance of hypoglycemia and lactic acidosis (neonatally, or later during fasting or induced by fructose) and may also be life-threatening.

9.1 Essential Fructosuria

9.1.1 Clinical Presentation

Essential fructosuria is a rare non-disease; it is detected by routine screening of urine for reducing sugars [1]. It is caused by a deficiency of fructokinase, also known as ketohexokinase (KHK), the first enzyme of the main fructose pathway (◘ Fig. 9.1).

9.1.2 Metabolic Derangement

Ingested fructose is partly (10–20%) excreted as such in the urine, the rest is slowly metabolized by an alternative pathway, namely conversion into fructose-6-phosphate by hexokinase in adipose tissue and muscle.

9.1.3 Genetics

The mode of inheritance is autosomal recessive and homozygote frequency has been estimated at 1:130,000. However, since the condition is asymptomatic and harmless, it may be more prevalent than reported.

The *KHK* gene is located on chromosome 2p23.3–23.2. Tissue-specific alternative splicing results in two isoforms, ketohexokinase A, widely distributed in most fetal and adult organs but with no clear physiological role, and ketohexokinase C, expressed in adult liver, kidney and small intestine, which is affected in essential fructosuria [2]. Two mutations of the *KHK* gene, G40R and A43T, both of which alter the same conserved region of fructokinase, have been detected and functionally characterized in a family with three compound heterozygotes [1].

9.1.4 Diagnosis

Fructose gives a positive test for reducing sugars and a negative reaction with glucose oxidase. It can be identified by various techniques, such as thin-layer chromatography, and quantified enzymatically. Fructosuria depends on the time and amount of fructose and sucrose intake and, thus, is inconstant. Fructose-tolerance tests (► Sect. 9.2) neither provoke an increase in blood glucose as in normal subjects, hypoglycemia or other changes as occur in HFI and FBPase deficiency, nor are metabolic changes in liver detectable by ^{31}P- magnetic resonance imaging (MRS) [3].

9.1.5 Treatment and Prognosis

Dietary treatment is not indicated, and the prognosis is excellent.

9.2 Hereditary Fructose Intolerance

9.2.1 Clinical Presentation

Infants, children and adults with hereditary fructose intolerance (HFI) are perfectly healthy and asymptomatic as long as they do not ingest food containing fructose, sucrose and/or sorbitol. Consequently, no metabolic derangement occurs during breast-feeding. The younger the child and the higher the dietary fructose load, the more severe the reaction. In the *acute* form of HFI, an affected newborn infant who is not breast-fed but receives a cow's milk formula sweetened and enriched with fructose or sucrose – formulas which should be obsolete today – is in danger of severe liver and kidney failure and death.

At weaning from breast-feeding or a fructose/saccharose-free infant formula, the first symptoms appear with the intake of fruits and vegetables [4, 5]. They are generally those of gastrointestinal discomfort, nausea, vomiting, restlessness, pallor, sweating, trembling, lethargy and, eventually, apathy, coma, jerks and convulsions. At this stage, laboratory signs may be those of acute liver failure and a generalized dysfunction of the renal proximal tubules. If the condition is unrecognized and fructose not excluded from the diet, the disease takes a *chronic*, undulating course with failure to thrive, liver disease manifested by hepatomegaly, jaundice, a bleeding tendency, edema, ascites, and signs of proximal renal tubular dysfunction. Laboratory findings are those of liver failure, proximal renal tubular dysfunction and derangements of intermediary metabolism. Note that hypoglycemia after fructose ingestion is

short-lived and can be easily missed or masked by concomitant glucose intake.

HFI can be suspected in an asymptomatic infant, if the parents have excluded certain foods from the diet, having becoming aware that they are not tolerated. In older children, a distinct aversion towards foods containing fructose may develop; these feeding habits protect them but are sometimes considered as neurotic behavior. At school age, HFI is occasionally recognized when hepatomegaly or growth delay is found [6]. Some adult cases were diagnosed after developing life-threatening reactions with infusions containing fructose, sorbitol or invert sugar (a mixture of glucose and fructose obtained by hydrolysis of sucrose) when these IV solutions were still in use [7]. Because approximately half of all adults with HFI are free of caries, the diagnosis has also been made by dentists. Although several hundred patients with HFI have been identified since its recognition as an inborn error of metabolism in 1957 [4], these observations indicate that affected subjects may remain undiagnosed and still have a normal life span.

9.2.2 Metabolic Derangement

HFI is caused by deficiency of the second enzyme of the fructose pathway, aldolase B (fructose 1,6-bisphosphate aldolase) (◘ Fig. 9.1), which splits fructose-1-phosphate (F-1-P) into dihydroxyacetone phosphate and glyceraldehyde and converts the triosephosphates into glucose and lactate. Moreover, as a consequence of the high activity of fructokinase, intake of fructose results in accumulation of F-1-P. This accumulation has two major effects [8]: *(i)* it inhibits the production of glucose by blocking gluconeogenesis and glycogenolysis, hence inducing hypoglycemia; *(ii)* it provokes overutilization and hence depletion of ATP, the energy currency of the cell, and of inorganic phosphate, utilized to regenerate ATP. The latter result in an increased production of uric acid, and a series of disturbances, including inhibition of protein synthesis and ultrastructural lesions, which are responsible for the hepatic and renal dysfunction. Recently, the accumulation of F-1-P has also been shown to result in deficient glycosylation of proteins, e.g., serum transferrin, by inhibiting phosphomannose isomerase [9] (► Chap. 41).

Residual activity measurable with fructose-1,6-bisphosphate as substrate (see below) is mainly due to the isozyme aldolase A. Thus, glycolysis and gluconeogenesis are not impaired in the fasted state in HFI patients.

It should be noted that the IV administration of fructose to normal subjects also induces the metabolic derangements described above (including the drop in ATP and inorganic phosphate, and rise in urate) to an equivalent extent, although they are more transient than in patients with HFI, as demonstrated by ^{31}P-MRS [3]. In normal subjects, IV fructose results in increased glycemia because of its rapid conversion into glucose. However, the equally rapid conversion of fructose into lactate may provoke metabolic acidosis. For these reasons, the use of fructose, sorbitol and invert sugar has been strongly discouraged for parenteral nutrition [10].

9.2.3 Genetics

Three different genes coding for aldolases have been identified. While isozymes A and C are mainly expressed in muscle and brain, respectively, aldolase B is the major fructaldolase of liver, renal cortex, and small intestine.

The human gene for aldolase B (*ALDOB*) has been mapped to chromosome 9q22.3. At present, according to the Human Gene Mutation Database, Cardiff (HGMD, http://uwcmml1s.uwcm.ac.uk/uwcm/mg/search/119669.html) and own data, approximately 30 causative mutations of the *ALDOB* gene have been reported. Among them, three amino acid substitutions, A150P[1], A175D, and N335K are relatively common among patients of central European descent and have been detected in 65%, 11% and 8% of mutated alleles, respectively [11, 12]. Some mutations may be found particularly in certain ethnic groups, such as the N335K and c.360-363 *del* CAAA mutations in the populations of the former Yugoslavia and Sicily, respectively. Since the three most common mutations are responsible for up to 84% of HFI cases in the European population [11, 12] and 68% of cases in North America [13] a non-invasive diagnostic approach using molecular genetic methods has been advocated and specific methods for the rapid concomitant detection of these frequent *ALDOB* mutations have been published [12, 14].

From molecular genetic neonatal screening studies in England and Germany, the prevalence of HFI has been calculated as 1:18,000 and 1:29,600, respectively [12, 15].

9.2.4 Diagnosis

Whenever HFI is suspected, fructose should be eliminated from the diet immediately. The beneficial clinical and chemical effects of withdrawal, usually seen within days, provide a first diagnostic clue. Laboratory findings will subsequently show a fall in the elevated serum transaminases and bilirubin, improved levels of blood clotting factors, and amelioration of proximal tubular dysfunction (proteinuria, mellituria, generalized hyperaminoaciduria, metabolic acidosis).

A cornerstone in the diagnosis of HFI is a careful nutritional history, with special emphasis on the time of weaning

[1] Note that the initiation codon ATG for methionine in *ALDOB* cDNA was ignored in previous designations and that, e.g., A150P was originally termed A149P.

when fruits and vegetables were introduced [5, 15, 16]. If the nutritional history is suggestive, or other aspects are indicative of HFI (e.g., a positive family history), the disorder should be confirmed by molecular diagnosis (► above) on DNA from peripheral leukocytes. This is a non-invasive approach and has the advantage over enzymatic measurement in liver tissue in that it eliminates the complication of secondarily lowered aldolase activity in a damaged liver.

If no mutation can be found despite a strong clinical and nutritional history suggestive of HFI, an enzymatic determination or a functional test should be undertaken after a few weeks of fructose exclusion. In liver biopsies from HFI patients, the capacity of aldolase to split F-1-P is reduced, usually to a few percent of normal (mean 5%, range 0–15%) [16], although residual activities as high as 30% of normal have been reported [7]. There is also a distinct (but less marked) reduction in the activity of aldolase toward fructose-1,6-bisphosphate (mean 17%, range 5-30%). As a consequence, the ratio of V_{max} towards fructose-1,6-bisphosphate versus the V_{max} towards F-1-P , which is approximately 1 in control liver, is increased to 2-∞ in HFI patients [16]. Aldolase activity is normal in blood cells, muscle, and skin fibroblasts, which contain a different isozyme, aldolase A. The enzymatic determination of aldolase B in small intestinal mucosa is discouraged. For post-mortem diagnosis, molecular studies and measurements of enzyme activity in liver and kidney cortex should be done. Of note, the level of residual activity has never been shown to correlate with the degree of tolerance to fructose.

In vivo handling of fructose is best reflected by a fructose tolerance test, in which fructose (200 mg/kg body weight) is injected as a 20% solution intravenously within 2 minutes. Blood samples are taken at 0 (2), 5, 10, 15, 30, 45, 60 and 90 minutes for determination of glucose and phosphate. In normal subjects, blood glucose increases by 0–40%, with no or minimal changes in phosphate [16]. In HFI patients, glucose and phosphate decrease within 10–20 minutes. As a rule, the decrease of phosphate precedes and occurs more rapidly than that of glucose. The test should be undertaken in a metabolic center, with careful monitoring of glucose and an indwelling catheter for the (exceptional) case of symptomatic hypoglycemia and its treatment by IV glucose administration. Oral fructose tolerance tests are not recommended, because they provoke more ill effects and are less reliable [16].

9.2.5 Differential Diagnosis

A high degree of diagnostic awareness is often needed in HFI because the spectrum of symptoms and signs is wide and nonspecific; HFI has been misdiagnosed as pyloric stenosis, gastroesophageal reflux, galactosemia, tyrosinemia, intrauterine infections, glycogen and other storage disorders, ornithine transcarbamoylase deficiency, and later in life as Wilson disease, leukemia, and growth retardation. Fructosuria may be secondary to liver damage, e.g., in tyrosinemia. Fructose malabsorption is frequently confused with HFI. Its metabolic basis is not well understood, but it is probably due to a defective fructose transporter in the small intestine, and the ingestion of fructose, and to a considerable lesser extent of sucrose, leads to abdominal pain and diarrhea. Since this condition is diagnosed by breath hydrogen analysis after an oral load of fructose, HFI has certainly to be excluded before such a tolerance test is performed. In sucrase-isomaltase deficiency, the ingestion of sucrose results in bloating, abdominal cramps and fermentative osmotic diarrhea; free fructose, however, is well tolerated.

9.2.6 Treatment and Prognosis

In acute intoxication, intensive care may be required and supportive measures such as fresh frozen plasma may be needed. The main therapeutic step in HFI, however, is the immediate elimination of all sources of fructose from the diet. This involves the avoidance of all types of food in which fructose, sucrose and/or sorbitol occur naturally or have been added during processing. It should be borne in mind that fructose and sorbitol may be present in medications (e.g., syrups, immunoglobulin solutions, rinsing fluids, enema solutions) and infant formulas (without adequate declaration of the carbohydrate composition). In this respect, it is deplorable that European Union regulations allow infant formulae to contain up to 20% of their total carbohydrate content as sucrose [17].

Sucrose should be replaced by glucose, maltose and/or starch to prevent the fructose-free diet from containing too much fat. Despite the availability of books and online information on food composition, a dietician should be consulted and practical aspects of the diet (e.g., the considerable variability of the fructose content of different food types, and the influence of storage temperature or method of preparation and manner of cooking on bioavailability) be discussed. Substitution of vitamins, especially ascorbic acid and folates, in the form of a multivitamin preparation should be prescribed to make up for their lack of intake from fruits and vegetables.

After institution of a fructose-free diet most abnormalities disappear rapidly, except for hepatomegaly, which may persist for months or even years [18]. The reason for this is unclear. Different thresholds of fructose intake for the development of certain symptoms have appeared in the literature, ranging from 40–250 mg/kg/day as compared with an average intake of 1–2 g/kg/day in Western societies [15]. Insufficient restriction of fructose has been reported to cause isolated growth retardation, as evidenced by catch-up growth on a stricter diet [6], but this observation has been questioned [19]. It has also to be kept in mind that

recommendations for maximum doses have not been validated in different genotypes and that sensitivity is known to be different in individual patients. Thus, it should be suggested to parents that they keep fructose intake as low as possible and that, at least in childhood, it should not be determined by subjective tolerance. For dietary control, the regular taking of the nutritional history is still best, as there are no good sensitive chemical parameters except, perhaps, transaminases. Quantification of carbohydrate-deficient proteins, e.g., transferrin, has been suggested for dietary monitoring; however, it is questionable whether this is a sufficiently sensitive procedure. Needless to say, patients (and their parents) should be made aware of the fact that infusions containing fructose, sorbitol or invert sugar are life-threatening, and that they should report fructose intolerance on any hospital admission. The prognosis is excellent with normal growth, intelligence and life span.

9.3 Fructose-1,6-Bisphosphatase Deficiency

9.3.1 Clinical Presentation

In about half of all cases, fructose-1,6-bisphosphatase (FBPase) deficiency presents in the first 1 to 4 days of life with severe hyperventilation caused by profound lactic acidosis and marked hypoglycemia. Later on, episodes of irritability, somnolescence or coma, apneic spells, dyspnea and tachycardia, muscular hypotonia, and moderate hepatomegaly may occur. As reported in the first patient to be described [20], such episodes are typically triggered by a febrile episode accompanied by a refusal to feed and vomiting. Attacks may also follow ingestion of large amounts of fructose (~1 g/kg body weight in one dose) especially after a period of fasting. FBPase deficiency may be life-threatening and, as in HFI, administration of IV fructose is contraindicated and may lead to death. In between attacks, patients are usually well, although mild, intermittent or chronic acidosis may exist. The frequency of the attacks decreases with age, and the majority of survivors display normal somatic and psychomotor development [21].

Most affected children experience a number of acute attacks before the diagnosis is made. Once diagnosis is established and treatment begins, the course is favorable.

In contrast to HFI, chronic ingestion of fructose does not lead to gastrointestinal symptoms – hence there is no aversion to sweet foods – or failure to thrive, and only exceptionally is there disturbed liver function.

Analysis of plasma during acute episodes reveals lactate accumulation (up to 15–25 mM) accompanied by a decreased pH and an increased lactate/pyruvate ratio (up to 30), hyperalaninemia and glucagon-resistant hypoglycemia. Hyperketonemia may be found, but in several patients ketosis has been reported to be moderate or absent (▶ below and [22]). Increased levels of free fatty acids and uric acid may also be found. Urinary analysis reveals increased lactate, alanine, glycerol, and, in most cases, ketones and glycerol-3-phosphate.

9.3.2 Metabolic Derangement

Deficiency of FBPase, a key enzyme in gluconeogenesis, impairs the formation of glucose from all gluconeogenic precursors, including dietary fructose (◘ Fig. 9.1). Consequently, maintenance of normoglycemia in patients with the defect is exclusively dependent on glucose (and galactose) intake and degradation of hepatic glycogen. Also, hypoglycemia is likely to occur when glycogen reserves are limited (as in newborns) or exhausted (as when fasting). The defect moreover provokes accumulation of the gluconeogenic substrates lactate/pyruvate, glycerol and alanine. The lactate/pyruvate ratio is usually increased, owing to secondary impairment of the conversion of 1,3-bisphosphoglycerate into glyceraldehyde-3-phosphate, resulting in accumulation of reduced nicotinamide adenine dinucleotide, the other substrate of glyceraldehyde-3-phosphate dehydrogenase (not shown in Fig. 9.1). Attention has been drawn to the fact that hyperketonemia and ketonuria, which usually accompany hypoglycemia, may be absent in some patients with FBPase deficiency [22]. This may be explained by pyruvate accumulation resulting in an increase of oxaloacetate and, hence, in the diversion of acetyl-coenzyme A (CoA) away from ketone-body formation into citrate synthesis. This, in turn, results in increased synthesis of malonyl-CoA in the cytosol. Elevated malonyl-CoA, by inhibiting carnitine-palmitoyl transferase I, prevents the entry of long-chain fatty-acyl-CoA into the mitochondria and, thereby, further reduces ketogenesis. It also promotes accumulation of fatty acids in liver and plasma, as documented in some patients.

Children with FBPase deficiency generally tolerate sweet foods, up to 2 g fructose/kg body weight per day, when given regularly distributed over the day and, in contrast to subjects with HFI, thrive on such a diet. Nevertheless, loading tests with fructose do induce hypoglycemia, as in HFI. This is caused by the inhibitory effect of the rapidly formed but slowly metabolized F-1-P on liver glycogen phosphorylase a. That higher doses of fructose are required for hypoglycemia to occur is explained by the fact that, in contrast to the aldolase-B defect, the FBPase deficiency still allows F-1-P to be converted into lactate. ^{31}P-MRS of the liver following IV administration of fructose (200 mg/kg b.w.) has documented a slower decrease in the fructose-induced accumulation of F-1-P and a delayed recovery of the ensuing depletion of Pi and ATP (both of which are signs of fructose toxicity) in patients with FBPase deficiency compared with healthy controls [3].

9.3.3 Genetics

FBPase deficiency is an autosomal-recessive disorder. Its frequency seems to be much lower than that of HFI; a first estimation of 1:350,000 has recently been reported for the Netherlands [21]. In addition to European and North American patients, many cases have been diagnosed in Japan. The high proportion of Turkish patients in our own series might simply be the result of the high rate of parental consanguinity.

There is evidence for the existence of more than one isozyme with FBPase activity in humans. The muscle isoform has different kinetic characteristics to the liver isoform and is not affected in patients with FBPase deficiency. Only the liver-type isoform gene (*FBP1*) has been cloned and characterized to date. It has been localized to chromosome 9q22.2–q22.3. *FBP1* mutations were first reported in 1995 [23], and to date 22 different mutations have been published. Among them are single nucleotide exchanges, small deletions and insertions, and one gross deletion. All regions of the gene may be affected and, with the exception of the c.961 *ins* G mutation, which has been reported to be responsible for 46% of mutated alleles in Japan [24], no single mutation is particularly frequent.

There are several FBPase-deficient patients in whom no mutation could be found affecting the coding region of *FBP1*. Therefore, it has been supposed that these patients carry mutations within the promoter region of *FBP1* or, more hypothetically, in the gene for the bifunctional enzyme which controls the concentration of fructose-2,6-bisphosphate, the main physiological regulator of FBPase [25].

9.3.5 Diagnosis

Whenever possible, the diagnosis of FBPase deficiency should be made by molecular analysis on DNA from peripheral leukocytes. If no mutation is found despite highly suggestive clinical and laboratory findings, the determination of enzymatic activity in a liver biopsy should be undertaken. In symptomatic cases, the residual activity may vary from zero to 30% of normal, indicating genetic heterogeneity of the disorder. Obligate heterozygotes have intermediate activity. Diagnosis can also be attempted in leukocytes, bearing in mind that deficient activity is diagnostic but that normal activity does not rule out FBPase deficiency in the liver [26]. Cultured skin fibroblasts, amniotic fluid cells and chorionic villi do not exhibit FBPase activity.

Loading tests with fructose (or with glycerol or alanine) or fasting tests should not form part of the initial investigations as they provide only a tentative diagnosis. However, such functional tests may be useful, and may point to a disturbance in the regulation of the fructose 6-phosphate-fructose-1,6-bisphosphate substrate cycle if mutation analysis and enzyme activity are normal despite a strong clinical and chemical suspicion of FBPase deficiency.

9.3.6 Differential Diagnosis

Other disturbances in gluconeogenesis have to be considered, including *(i)* pyruvate dehydrogenase deficiency characterized by a low lactate/pyruvate ratio and aggravation of lactic acidosis by glucose infusion; *(ii)* pyruvate carboxylase deficiency; *(iii)* phosphoenol pyruvate carboxykinase deficiency; *(iv)* respiratory chain disorders; *(v)* glycogenosis types Ia and Ib characterized by hepatonephromegaly, hyperlipidemia and hyperuricemia.

9.3.7 Treatment and Prognosis

Whenever FBPase deficiency is suspected, adequate amounts of IV or oral glucose should be given. The acute, life-threatening episodes should be treated with an IV bolus of 20% glucose followed by a continuous infusion of glucose at high rates (10-12 mg/kg/min for newborns) and bicarbonate to control hypoglycemia and acidosis.

Maintenance therapy should be aimed at avoiding fasting, particularly during febrile episodes. This involves frequent feeding, the use of slowly absorbed carbohydrates (such as uncooked starch), and a gastric drip, if necessary. In small children, restriction of fructose, sucrose and sorbitol is also recommended, as are restrictions of fat, to 20–25%, and protein to 10% of energy requirements. In the absence of any triggering effects leading to metabolic decompensation, individuals with FBPase deficiency are healthy and no carbohydrate supplements are needed.

Once FBPase deficiency has been diagnosed and adequate management introduced, its course is usually benign. Growth and psychomotor and intellectual development are unimpaired, and tolerance to fasting improves with age up to the point that the disorder does not present a problem in later life. This might be explained by an increasing capacity to store glycogen in the liver, resulting in a lesser dependence on gluconeogenesis for the maintenance of blood glucose. Many patients become obese because their concerned parents overfeed them and because later they continue these eating habits. However, under carefully observed conditions, a hypocaloric diet can lead to a considerable weight loss in obese patients without lactic acidosis and hypoglycemia [Steinmann, personal observations].

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