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ORIGINAL ARTICLE

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Fructose-1,6-bisphosphatase deficiency causes fatty liver disease and requires long-term hepatic follow-up

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Abstract

Liver disease, occurring during pediatric or adult age, is often of undetermined cause. Some cases are probably related to undiagnosed inherited metabolic disorders. Hepatic disorders associated with fructose-1,6-bisphosphatase deficiency, a gluconeogenesis defect, are not reported in the literature. These symptoms are mainly described during acute crises, and many reports do not mention them because hypoglycemia and hyperlactatemia are more frequently in the forefront. Herein, the liver manifestations of 18 patients affected with fructose-1,6-bisphosphatase deficiency are described and the corresponding literature is reviewed. Interestingly, all 18 patients had liver abnormalities either during follow-up (hepatomegaly [n = 8/18], elevation of transaminases [n = 6/15], bright liver [n = 7/11]) or during acute crises (hepatomegaly [n = 10/17], elevation of transaminases [n = 13/16], acute liver failure [n = 6/14], bright liver [n = 4/14]). Initial reports described cases of liver steatosis, when liver biopsy

was necessary to confirm the diagnosis by an enzymatic study. There is no clear pathophysiological basis for this fatty liver disease but we postulate that endoplasmic reticulum stress and de novo lipogenesis activation could be key factors, as observed in *FBP1* knockout mice. Liver steatosis may expose patients to severe long-term liver complications. As hypoglycemia becomes less frequent with age, most adult patients are no longer monitored by hepatologist. Signs of fructose-1,6-bisphosphatase deficiency may be subtle and can be missed in childhood. We suggest that fructose-1,6-bisphosphatase deficiency should be considered as an etiology of hepatic steatosis, and a liver monitoring protocol should be set up for these patients, during lifelong follow-up.

KEYWORDS

acute liver failure, bright liver, fatty liver disease, fructose-1,6-bisphosphatase deficiency, gluconeogenesis defect, hypoglycemia, lactic acidosis

1 | INTRODUCTION

Gluconeogenesis is a metabolic pathway that results in the synthesis of glucose from glucose-forming substrates. It is activated after a moderate period of fasting in adults but more quickly in newborns or young children, who do not have sufficient glycogen stocks to provide their glucose needs through glycogenolysis only. Gluconeogenesis occurs mainly in the liver. The specific enzyme fructose-1,6-bisphosphatase 1, which catalyzes the dephosphorylation of fructose-1,6-bisphosphate to fructose-6-phosphate, is an irreversible key step of this pathway.

Fructose-1,6-bisphophatase (FBPase) deficiency is an autosomal recessive disorder due to mutations in the *FBP1* gene,[1] first described in 1970.[2] The disease is rare, with an estimated incidence between 1/350 000 and 1/900 000.[3]

In most cases, disease manifestations appear before the age of two, and usually from the first day of life. The main symptoms are prolonged fasting hypoglycemia with severe lactic acidosis.[4] There is an increase in serum glycerol level, resulting in false hypertriglyceridemia. Infections, prolonged fasting or massive fructose ingestion can trigger acute crises. Apart from acute crises, children often remain asymptomatic, with normal psychomotor development and growth. With aging, fasting tolerance increases and the frequency of hypoglycemia becomes very low. Determination of FBPase 1 activity in lymphocytes, and molecular analysis of the *FBP1* gene allow to confirm the diagnosis.

Hypoglycemia is easily corrected and prevented with glucose supplementation. Prevention of acute crises requires limitation of fasting using raw cornstarch or enteral nutrition and limited fructose diet.

Liver disease symptoms have been reported in FBPase deficiency, but they are poorly characterized and were not systematically investigated, especially during follow-up.

We report liver disorders of FBPase deficiency found in 18 patients diagnosed in France. Symptoms found at the time of acute crises as well as persistent hepatic abnormalities during long-term follow-up are presented.

2 | METHODS

A retrospective study was conducted in France, according to the French ethic and regulatory law for medical research. The inclusion criterion was a diagnosis of FBPase deficiency supported by the detection of biallelic pathogenic variants in the *FBP1* gene. The patients were included using the database of patients with FBPase deficiency from the Bicêtre's Hospital biochemistry laboratory (France), with their agreement and the approval of the patients and their clinical physicians. The patients' clinical, biological, and radiological features were collected retrospectively from initial and follow-up medical records.

3 | RESULTS

We recorded medical data from 18 patients with FBPase deficiency, all diagnosed in French centers (Table 1). Eight out of these 18 patients had already been reported by Lebigot et al[4] in 2015 (Table S1).

The first acute crises occurred in the first days of life in eight patients. Age at first manifestation ranged from 6 months to 2.5 years in 10 patients. In most cases, hypoglycemia with lactic acidosis (n = 14/18) was the main feature, but Reye-like syndrome with lactic acidosis (n = 2/18), or lactic acidosis without hypoglycemia (n = 2/18) were also observed.

TABLE 1 Clinical and genetic data of patients

	General findings							
	Current age	**Age at first crises**	**Gender**	**Consanguinity**	**Age at molecular diagnosis**	**Major symptoms at first crises**	**Number of acute crises**	***FBP1* variants NM_000507, NC_000009.11**
Patient 1	5 years	8 mo	M	Yes	3 years 6 months	Hypoglycemia, lactic acidosis	3	c.[685C>T;902_904del]
Patient 2	6 years	9 mo	M	No	2 years	Hypoglycemia, lactic acidosis	3	c.[685C>T;902_904del]
Patient 3	4 years	H9	M	No	2 years	Hypoglycemia, lactic acidosis	3	c.[639C>G;778G>A]
Patient 4	20 years	24 mo	M	No	2 years	Hypoglycemia, lactic acidosis	6	c.[48del;472C>T]
Patient 5	7 years	30 mo	M	Yes	3 years 6 months	Hypoglycemia, lactic acidosis	3	c.[704dup;704dup]
Patient 6	10 years	12 mo	F	Yes	4 years 9 months	Hypoglycemia, lactic acidosis	3	c.[685C>T;685C>T]
Patient 7	5 years	H15	M	Yes	5 months	Hypoglycemia, lactic acidosis	4	c.[577dup;577dup]
Patient 8	12 mo	H22	F	No	1 month	Hypoglycemia, lactic acidosis	1	c.[825+1G>A;(?_-86)_(170+172_171-?)del]
Patient 9	22 mo	H12	M	Yes	20 months	Lactic acidosis	3	c. [(?_-86)_(170+172_171-?)del;(?_-86)_(170+172_171-?)del]
Patient 10	7 mo	H22	M	Yes	7 months	Hypoglycemia, lactic acidosis	2	c. [(?_-86)_(170+172_171-?)del;(?_-86)_(170+172_171-?)del]
Patient 11	3 years	H24	M	Yes	2 years 3 months	Hypoglycemia, lactic acidosis	4	c.[685C>T;685C>T]
Patient 12	8 years	7 mo	F	Yes	14 months	Hypovolemic shock, lactic acidosis	7	c.[685C>T;685C>T]
Patient 13	19 years	H26	M	No	9 years	Hypoglycemia, lactic acidosis	5	c.825+1G>A;960_961insG]
Patient 14	12 years	6 mo	M	Yes	16 months	Hypoglycemia, lactic acidosis	3	c.[685C>T;685C>T]
Patient 15	14 years	14 mo	F	Yes	3 years	Reye syndrome, lactic acidosis	10	c.[731_738delins20;731_738delins20]
Patient 16	21 years	H22	F	Yes	18 months	Hypoglycemia, lactic acidosis	10	c.[685C>T;685C>T]
Patient 17	17 years	14 mo	M	No	16 months	Hypoglycemia, lactic acidosis	5	c.[639C>G;(?_-86)_(170+172_171-?)del]
Patient 18	9 years	10 mo	M	Yes	30 months	Hypoglycemia, lactic acidosis, Reye syndrome	6	g.[97 364 754_97 382 011del;97 364 754_97 382 011del]

Abbreviations: H, hours; mo, months.

The genetic diagnosis was done between the ages of 1 month and 4 years and 9 months, with an average delay of 19 months between first acute crises and diagnosis. Seventeen out of 19 patients had an enzyme activity assay performed on peripheral blood mononuclear cells, and one patient on hepatocytes showed collapsed FBPase 1 activity compared to the control. All patients received genetic diagnostic confirmation by identification of pathogenic *FBP1* variants, either homozygous or compound heterozygous.

All patients (n = 18/18) showed hepatic manifestations (Table 2). When observed at the time of acute crises, these manifestations included:

- Hepatomegaly (n = 10/17), sometimes voluminous (n = 3/10) mimicking a glycogen storage disease type I (GSDI). Rapid spontaneous regression of hepatomegaly was observed with dietary treatment.
- Increased transaminases (n = 13/17), sometimes more than 10 times the upper normal limit (n = 5/13), mimicking acute hepatitis.
- Acute liver failure (6/14). Prothrombin time values in these six patients ranged from 57% to 27%. Quick recovery followed correction of hypoglycemia and lactic acidosis. For two patients, diagnosis of Reye's syndrome was retained. Despite liver failure and/or severe hepatitis, the bilirubin level remained normal in all patients.
- Bright liver (6/14) on abdominal ultrasound.

Hepatic manifestations observed during the follow-up, that is, in the chronic phase of the disease, were:

- Hepatomegaly, persisting after metabolic decompensations, in six patients. Hepatomegaly occurred without any decompensation in two patients.
- A fluctuating increase in liver enzymes, usually less elevated than during the decompensation period (6/15).
- Eleven patients had at least one liver ultrasound. In seven of them, bright liver was observed, often associated with hepatomegaly (4/7). Bright liver was homogeneous (5/7) or inhomogeneous (2/7).

The average follow-up time was 7.8 years (7 months-19 years).

In total, among the 18 patients, 17 had at least one liver ultrasound, during acute crisis or follow-up. For 11 of them, bright liver was observed.

Only one patient had a liver biopsy, which revealed a clarified aspect of hepatocytes and rare non-arciform fibrous septa from rare portal spaces.

Finally, several patients became overweight (n = 4/18) over time (shown in Table 2).

4 | DISCUSSION

To our knowledge, our report is the first series of individuals affected with FBPase deficiency with review of the long-term liver symptoms.

Liver symptoms have regularly been reported in the literature during acute crisis. However, they are poorly characterized and were not systematically investigated, especially during follow-up.

Hepatomegaly and moderate transaminases increase is the most common feature.[5-10] Nevertheless, neither the presence nor the absence of hepatomegaly or the possible regressive evolution are indicated in many published series.

Severe liver symptoms over at least one decompensation were observed in 55% of our patients. The voluminous, soft, and painless hepatomegaly presented by three patients, and the highly increased transaminases blood levels mimicking acute hepatitis without jaundice, cannot be attributed to a common viral infection. These symptoms probably occur when liver metabolic suffering and energy deficiency are more pronounced.

We observed increased prothrombin time in six patients. Some patients have also been reported in the literature with disturbed liver function[11-14] and Reye's syndrome.[4,15,16] One of these patients presented Reye-like syndrome when he was 20 years old.[12] The pathophysiological mechanism of hepatic failure has not yet been elucidated.

In our cohort, 60% of patients had liver brightness on a sonography during an acute crisis and/or during follow-up. Abdominal ultrasound without description of brightness has been reported in two studies,[3,17] and two papers describe a bright liver sonography.[18,19] Kılıç et al[19] describe hepatosteatosis on ultrasound in 7 out of 10 patients at the time of diagnosis. They do not provide follow-up information. The pathophysiology of this steatosis is not known. In our cases, it does not seem to be linked with the age at first crises, the numbers and severity of decompensations, nor with the presence of additional liver symptoms.

Bright liver on sonography may reflect hepatic steatosis. In the past, patients described with FBPase deficiency were diagnosed with enzymatic studies performed on liver biopsy to determine the activity of FBPase 1. Among these, histological exams were found to show hepatic steatosis[2,5,19-26] described as mild to moderate in some patients,[22-24] severe in others.[5,25-27] At present, the study of enzymatic activity on lymphocytes[28] and the sequencing of *FBP1* gene[1,29] led to a dramatic reduction in the number of liver biopsies. The presence of hepatic steatosis has therefore rarely been reported in recent articles.[10,30,31] Only two articles described fatty liver disease, as macrovesicular steatosis in these patients.[10,30]

TABLE 2 Major hepatic manifestations during decompensations and follow-up

	Decompensations				Follow-up			
	Hepatomegaly	ASAT/ ALAT	PT/FV	Ultrasounds findings	Hepatomegaly	ASAT/ ALAT	Ultrasounds findings	Other findings
Patient 1	Yes	>10 N	79%/NR	HPM HE	Yes	NR	HPM HE	
Patient 2	No	>10 N	42%/57%	N	No	N	HE	Overweight
Patient 3	No	N	NR	N	No	2-10 N	HE	
Patient 4	No	2-10 N	NR	NR	No	N	NR	
Patient 5	Yes	2-10 N	69%/NR	HPM HE	No	NR	N	Overweight
Patient 6	NR	NR	NR	NR	Yes	N	HE	Fibrosis on biopsy
Patient 7	No	2-10 N	70%/NR	HE	No	2-10 N	HE	
Patient 8	Yes	N	NR	N	Yes	NR	NR	
Patient 9	Yes	N	71%/NR	N	Yes	2-10 N	NR	
Patient 10	No	NR	N	NR	Yes	2-10 N	HPM HE	
Patient 11	Yes	>10 N	57%/35%	HPM HE	Yes	2-10 N	NR	
Patient 12	No	2-10 N	77%/NR	N	No	N	NR	Overweight
Patient 13	Yes	2-10 N	58%/NR	N	No	N	NR	
Patient 14	Yes	>10 N	89%/84%	HPM HE	Yes	N	N	Overweight
Patient 15	Yes	>10 N	27%/NR	HPM	No	N	NR	
Patient 16	Yes	2-10 N	54%/50%	N	No	N	N	
Patient 17	Yes	2-10 N	73%/NR	HPM HE	No	N	N	
Patient 18	No	2-10 N	49%/98%	NR	Yes	N	HPM HE	

Abbreviations: ASAT/ALAT, aspartate aminotransferase/alanin aminotransferase; HE, hyperechogenicity; HPM, hepatomegaly; N, normal; NR, not reported; PT, prothrombin time.

The steatosis can progress to fibrosis. Three cases of liver fibrosis have been reported, including two cases of moderate periportal fibrosis[5] and one of extensive fibrosis.[11] The only patient in our cohort who had a liver biopsy also had some non-arciform fibrous septa. There are no data on the long-term follow-up of this steatosis/fibrosis. As described in other causes of persistent steatosis, that is, nonalcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH), adenoma or hepatocellular carcinoma might occur during long-term evolution.

Several hypotheses regarding the pathophysiology of this steatosis can be discussed. Disruption of the *fbp1* gene in mice[32] alters liver metabolic homeostasis and supports tumorigenesis, through activation of endoplasmic reticulum (ER) stress, a mechanism also involved in NAFLD,[33] and through evolution of stellate cells to senescence. These mutant mice develop hepatomegaly and steatosis, with triglyceride accumulation and enzymes of de novo lipogenesis activation. Similar mechanisms may operate in FBPase 1 deficient patients during decompensation, due to "metabolic stress."

Moreover, FBPase 1 has a noncanonical function: when located in the nucleus, it acts as a transcription factor.[34] In kidney cancer cells, this function reduces HIF (hypoxic-inductible-factors)-induced expression of glycolytic genes. In these cells, *FBP1* acts as a tumor suppressor gene.[35] Whether this function is also impaired in our patients is unknown, it could participate in the chronic clinical phenotype and their long-term evolution.

Steatosis is described in numerous inherited metabolic disorders, but with no clear explanations in general.[36,37] Mice with phosphoenolpyruvate carboxykinase (PEPCK) deficiency, another gluconeogenesis defect, also develop severe steatosis, attributed to accumulation of triglycerides.[38] In hereditary fructose intolerance, the steatosis would be secondary to the accumulation of fructose-1-phosphate.[39] This molecule does not accumulate in FBPase deficiency, except in case of fructose load.

In glycogen storage disease type 1 (GSD1), the most frequent gluconeogenesis disorder, hepatic steatosis is frequent and is mainly due to a stimulation of lipogenesis by glucose-6-phosphate. It can be complicated by hepatic adenomas that can progress to hepatocarcinoma, even in

the absence of cirrhosis.[40,41] Lifelong regular ultrasounds and scan monitoring are therefore recommended in patients with GSD1.[42]

Four of our patients are overweight, which is an additional risk factor for steatosis or steatohepatitis. Dietary management should prevent overweightedness and additional fatty liver disease.

In the same way, the following guidelines for hepatic management of patients with FBPase deficiency can be proposed. During acute crises, we recommend, for all patients, to check for liver function, blood coagulation, and liver sonography if they have hepatomegaly. During the follow-up, we recommend carrying out a liver blood check-up, an AFP testing and an abdominal ultrasound once a year, specifying the search for bright liver and liver tumor. Fibrosis assessment should also be regularly performed using noninvasive imaging tests such as transient elastography. These patients should be considered as patients with chronic liver disease and would benefit from the usual surveillance and prevention recommended for this disease. If hepatic fibrosis is identified, a close follow-up should be planned with a liver ultrasound every 6 months in order to early detect hepatocellular carcinoma.

Very long-term follow-up of chronic diseases beginning during the childhood is usually difficult to obtain, in particular for a disorder considered as benign in adults. Prospective follow-up of patients, including in adulthood, could provide an insight into the real evolution of these patients, who are said to be doing well, but whose long-term future is unknown. Finally, we suggest that FBPase deficiency should be added to the list of etiologies of hepatic steatosis.[36,43]

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Magali Gorce: Conception, design, analysis, interpretation of data, drafting the article. **Elise Lebigot**: Analysis and interpretation of data, revising critically the article. **Alina Arion**: Analysis, interpretation of data. **Anais Brassier**: Analysis, interpretation of data. **Aline Cano**: Analysis, interpretation of data. **Pascale De Lonlay**: Analysis, interpretation of data. **François Feillet**: Analysis, interpretation of data. **Claire Gay**: Analysis, interpretation of data. **François Labarthe**: analysis, interpretation of data. **Marie-Cécile Nassogne**: Analysis, interpretation of data. **Sandrine Roche**: Analysis, interpretation of data. **Agathe Roubertie**: Analysis, interpretation of data. **Elise Sacaze**: Analysis, interpretation of data. **Guy Touati**: Analysis, interpretation of data, revising critically the article. **Pierre Broué**: Conception, design, analysis, interpretation of data, revising critically the article, guarantor.

DATA AVAILABILITY STATEMENT

Data archiving is not mandated but data will be made available on reasonable request.

ETHICS STATEMENTS

According to the French ethic and regulatory law (public health code) retrospective studies based on the exploitation of usual care data do not should be submit at an ethic committee but they have to be declare or cover by reference methodology of the French National Commission for Informatics and Liberties (CNIL). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

ANIMAL RIGHTS

This article does not contain any studies with animal subjects performed by the any of the authors.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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