Eur J Pediatr (1983) 140 : 283–288

European Journal of
Pediatrics

Review

Glycogen storage disease type Ib*

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Abstract. Glycogen storage disease type Ib has all the clinical manifestations of glycogen storage disease type Ia such as hepatomegaly, growth retardation, bleeding tendency, hypoglycemia, hyperlactacidemia, hyperuricemia, hyperlipidemia, impaired platelet function *plus* neutropenia. The overall glucose-6-phosphatase activity in disrupted microsomes from liver is normal whereas glucose-6-phosphate translocase, the first enzyme in the glucose-6-phosphate transport system is absent. There is no glucose-6-phosphatase activity in vivo. Recent results show that in granulocytes the glucose-6-phosphate-dependent hexosemonophosphate-shunt is impaired.

Key words: Glycogen storage disease

Introduction

Glycogen storage disease (GSD) type I is characterized by hepatomegaly, growth retardation, bleeding tendency, hypoglycemia, hyperlactacidemia, absence of ketosis, hyperuricemia, hyperlipidemia and impaired platelet function [28]. The enzyme defect was first described by Cori and Cori [17] in 1952. Glucose-6-phosphatase of the liver is absent when the assay is performed on a frozen liver sample.

Since 1959 an increasing number of cases of glycogen storage disease type I have been described in which liver glucose-6-phosphatase was normal when assayed in a frozen liver samples. Until 1983 at least 37 patients with this disorder were described and 6 more have been diagnosed by the authors. The following article gives a review of the findings of this interesting, hereditary error of glycogen metabolism.

Historical aspects and nomenclature

H. G. Hers reported in 1959 at the IX. International Congress of Pediatrics in Montreal on a patient with glycogen storage disease type I in whom he found normal activity of glucose-6-phosphatase in frozen liver (Table 1). The first publication on this combination appeared in the same year [35]. In 1968 Senior and Loridan [53, 54] proposed the term glycogenosis type Ib for this disease and specified cases with absent activity in a frozen liver sample as type Ia. In a paper, presented at the Annual Meeting of the European Society for Pediatric Research in Rotterdam 1976, David et al. [18] used the term 'pseudotype I glycogenosis' for a patient (case No. 4) with clinical features of glycogenosis type I, normal activity of glucose-6-phosphatase in (frozen?) liver and a shortened half-life of double-labeled glucose in blood suggesting an increase in the recycling of glucose (see below). In 1980 [8, 34] pseudotype I glycogenosis was

Table 1. Cases of GSD Ib published and known to the authors

Case no.	Year of publication	Author and Reference No	Initials of the patient and sex	Glycogen content in liver	Leukocytes	Remarks
1	1959	Hers	–	–	–	
2	1959 1961 1962	Lowe et al. [35] Sokal et al. [56] Lowe et al. [36]	J.B. male	8.6%	–	
3	1964	Briggs and Haworth [10]	– female	10.0%	Normal	
4	1965 1968 1976	Francois et al. [20] Francois et al. [21] David et al. [18]	P.B. female	7.0%	–	Parents cousins of first grade Short half life of $^{3}H/^{14}C$ glucose Term Pseudotype I used
5	1967	Marchi et al. [37]	G.-Z. male	9.5%	–	
6	1967 1972 1972	Badoual and Lestradet [4] Badoual et al. [5] Grenet et al. [24]	C.K. male	7.0%	–	Frequent respiratory infections
7	1968 1968	Senior and Loridan [53] Senior and Loridan [54]	Y.B. male	7.7%	–	Term GSD Ib for the first time

* Prof. Horst Bickel on the occasion of his 65th birthday

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Table 1 (continued)

Case no.	Year of publication	Author and Reference No	Initials of the patient and sex	Glycogen content in liver	Leukocytes	Remarks
8	1970	Sadeghi-Nejad et al. [49]	S.G. female	10.2%	–	
9	1971	Spencer-Peet et al. [57]	18 female	18.5%	–	Elder sister of patient 10
10			19 male	5.9%	–	'Chest infections'
11			20 male	9.8%	–	
12	1973 1981	Moses [40] Moses [41]	Y.B. male	8.0%	–	First cousin marriage Short half-life of $^{3}H/^{14}C$ glucose
13	1974	Ragab et al. [46]	–	–	Neutropenia	First association between GSD
14						Ib and neutropenia documented
15	1977	Bialek et al. [9]	–	–	Neutropenia	
16						
17	1977	Bürdehl et al. [11]	A.G. female	10.3%	Granulozytopenia	
18	1978	Rosenfeld et al. [48]	M.A. male	7.7%	–	
19			S.G. female	11.7%	–	
20	1978	Chalmers et al. [12]	– male	13.0%	Normal	
21	1978 1979 1981 1982	Narisawa et al. [42] Igarashi et al. [32] Narisawa et al. [43] Narisawa et al. [44]	Y.S. female	8.5%	Neutropenia	Episodes of infections
22	1980	Stegner et al. [58]	E.D. female	5.3%	Neutropenia	Episodes of infections
23	1980	Mc Cabe et al. [38]	– female	12.0%	Granulocytopenia	Frequent infections
24	1980	Sann et al. [50]	– female	11.3%	Granulocytopenia	Parents cousins
25	1980 1980 1980 1981	Beaudet et al. [7] Beaudet et al. [8] Lange et al. [34] Andersen et al. [1]	– male	7.3%	Granulocytopenia	Term GSD Ib synonym with Pseudotype I Recurret infections
26	1980 1981 1982 1983	Corbeel et al. [13] Corbeel et al. [14] Corbeel et al. [15] Corbeel et al. [16]	D.L. female	7.5%	Granulocytopenia	Portocaval shunt (PCS), Recurrent infections, Short half-life of $^{3}H/^{14}C$ (after PCS)
27	1980 1980 1983	Heyne and Gahr [25] Hayne and Gahr [26] Gahr and Heyne [22]	I.V. female	8.1%	Neutropenia	
28	1981	Schaub et al. [52]	T.M. male	10.0%	Granulocytopenia	Recurrent infections
29	1981	Bartram et al. [6]	E.P. female	8.2%	Granulocytopenia	
30	1981	Garibaldi [23]	– female	15.6%	–	
31	1981	Roe [47]	– male	–	Neutropenia	
32			– male	–	Neutropenia	
33	1981	Skaug et al. [55]	– male	6.8%	Granulocytopenia	Recurrent upper respiratory tract infections
34	1981	Narisawa et al. [43]	– –		Neutropenia	Frequent infections
35	1981 1982 1983	Narisawa et al. [43] Narisawa et al. [44] Kuzuya et al. [35]	Y.M. female	–	Normal	First adult patient, no infections, partial deficiency of translocase, mild from
36	1982	Mc Cabe et al. [39]	– male	–	Neutropenia	Portocaval shunt
37	1983	Seger et al. [51]	– –	–	Neutropenia	Cutaneous infections
38			E.-C. S female	7.0%	Granulocytopenia	
39			C.S. male	17.0%		
40			M.M.	6.5%	Granulocytopenia	Recurrent infections
41			M.B.	10.1%	Granulocytopenia	Pulmonary infections
42			B.H.	5.2%	Granulocytopenia	Recurrent infections
43			E.C. female	6.8%	Neutropenia	Recurrent infections

– not published, resp. not known

equated with GSD Ib although they were two different diseases affecting the half-life of double-labeled glucose in blood (see section 'special functional tests'). In 1974 Ragab et al. [46] were the first to become aware of 'maturation arrest' neutropenia in GSD Ib. Episodes of frequent respiratory infections had already been described in 1967 [4]. In the following years the interest of many investigators was focused on this neutropenia and the disturbance of granulocyte function. The exact enzyme defect in liver was described in 1980 [34]. G6P-translocase, one enzyme in the G6P-transport system has no measurable activity.

Clinical picture and metabolic characteristics

Type Ib has all the clinical manifestations of type Ia GSD plus two additional findings: (1) neutropenia; (2) failure to maintain blood glucose at a constant level after intravenous administration of glycerol [54]. In five cases 'ketonuria' [24, 55], 'acetonuria' [20, 27], 'urine ketone bodies' [10], 'ketosis' [10], 'breath smelled of acetone' [10, 20], 'ketotic hypoglycemia' [14], 'ketonemia' [55] were reported mostly during the first examination after emergency admission to the hospital. Ketonemia and ketonuria are not expected in glucose-6-phosphatase deficiency. In the five cases reported neither quantitative values of ketones are given nor were ketone measurements during loading tests performed. Thus, these findings remain unclear, retrospectively. Other functional tests with glucagon, epinephrine, glucose, galactose and fructose gave the same results as in GSD Ia, indicating that glucose cannot be released from G6P.

Special functional tests

The typical clinical features of glycogen storage disease type I and normal activity of glucose-6-phosphatase in a frozen liver sample lead to the assumption that the enzyme is not active in vivo.

An in vivo test of glucose-6-phosphatase in humans was published by van Hoof et al. and by Hue and Hers [30, 59]. It was based on the observation that the half-life of intravenously-injected, uniformly labeled ^{14}C-glucose is longer than the half-life of glucose labeled with tritium in position 2. Thus, the $^{3}H/^{14}C$ ratio of blood glucose decreased in a linear way.

According to the theory of the 'futile cycles' [31] the decrease of the $^{3}H/^{14}C$ ratio in blood glucose depends on the recycling of substrates and requires the operation of glucose-6-phosphatase from the liver. A 'futile cycle' is the simultaneous operation of two antagonistic conversions of which the net balance is the hydrolysis of ATP to ADP and inorganic phosphate. These futile cycles are probably potential sites of control of the glycolysis and the gluconeogenesis. They exist at the level of interconversion of pyruvate and phosphoenolpyruvate, where pyruvate carboxylase is reserved by pyruvate carboxykinase, at the level of interconversion of fructose diphosphate and fructose-6-phosphate, where phosphofructokinase is reserved by fructose diphosphatase and at the level of interconversion of glucose and glucose-6-phosphate, where glucokinase is reserved by glucose-6-phosphatase.

It could therefore be expected that in glycogen storage disease type I the dilution of double-labeled glucose with unlabeled glucose does not occur in the circulation, leading to no decrease of the $^{3}H/^{14}C$ ratio in blood glucose.

Indeed, in glycogen storage disease type Ia the ratio of $^{3}H/^{14}C$ in blood glucose is 100% after 30 min as well as after 60 min. In controls the $^{3}H/^{14}C$ ratio is 75% after 30 min and 50%–60% after 60 min. In eight patients with glycogen storage disease type Ib the 30 min value was 90%–97% and the 60 min value 90%–95% [29]. This demonstrates that glucose-6-phosphatase is not active in vivo in GSD type Ib. In Table 1a typical result of the double isotopic test in GSD Ib was reported in case 24 and known to the authors in case 35. However, six patients with the clinical and biochemical picture of GSD Ib are known [29], who have normal or greater decrease of the $^{3}H/^{14}C$ ratio ranging from 8%–65% 30 min after the injection. In Table 1 such a short half-life was reported for case 4, in case 9 it was 13% after 30 min, in case 26 30% after 30 min and in case 30 64% after 30 min. This variant was termed pseudotype I glycogenosis by David et al. [18] and by Hue [29]. The term pseudotype I glycogenosis was falsely equated to GSD Ib by Anderson et al. [1] and Beaudet et al. [8].

In case 26 [14] the $^{3}H/^{14}C$ test was unfortuately performed only 5 months after a portocaval shunt. If the results were the same before the portocaval shunt, this patient has to be classified as a pseudotype I glycogenosis.

At the moment, an explanation for the shortening of the half-life of double-labeled glucose in some cases of glycogenosis type I cannot be given. However, further studies should be focused on the secretion of insulin after glucagon or glucose in pseudotype I glycogenosis. Moses [40] was the first who reported in case 12 a marked serum insulin response after an intravenous glucose tolerance test, unlike the response in cases of GSD Ia, who are insulinopenic and show a diabetic pattern. In case 4 David et al. [18] could show that plasma insulin reaches values up to 1000 μU/ml after glucagon administration in pseudotype I glycogenosis but not in classical GSD Ia. In case 26 Corbeel et al. [14] could demonstrate during a glucose tolerance test an increase of insulin from 20–50 μU/ml after 120 min before the portocaval shunt and from 10–90 μU/ml after 60 min after the portocaval shunt. Possibly, shortening of the half-life of double-labeled glucose may be related to an increased insulin secretion rate in pseudotype I glycogenosis.

Examination of the granulocytic system

Since the first description in 1974 [46] neutropenia in GSD Ib has been almost a constantly reported feature of the disease. However, the extent of neutropenia varies greatly from mild neutropenic states to complete agranulocytosis. In the same manner their clinical expression varies, with a predominance of staphylococcal infections [1, 7, 8] and candidiasis [6, 38].

The neutropenia, usually constant or nearly constant, can show a cyclic behavior [11] and responds to lithium chloride in vitro [38], to triamcinolone at low doses in vivo [9], also to hydrocortisone and subcutaneous glucagon [47]. It shows no response to prednisone and anabolics [11]. There was no significant granulocytosis during bacterial infections and the effects of endotoxin and epinephrine stimulation of peripheral blood neutrophils was smaller than expected [1].

No antibodies on the surface of the neutrophils or in the serum were demonstrable [6]. There were also no apparent inhibitors of either granulocyte colony-forming units or 'granulopoietin' production present in the patients' serum [38].

The nature of the neutropenia is characterised by maturation arrest in the bone marrow [6, 11, 38, 46] with normal counts of colony forming marrow cells and with increased [46] or diminished [38] colony stimulating activity of peripheral blood cells. The two patients (cases No. 31 and 32) reported by Roe [47] showed mild granulocytic hyperplasia in bone marrow but no maturation arrest.

In case No. 29 [6] the content of colony forming units in culture as an indicator of the number of myelopoietic determined bone marrow stem cells was markedly reduced. This indicates an 'inherited' or 'congenital' neutropenia. Data from bone marrow examinations are summarised in Table 2.

Recent observations demonstrate the impairment of some functional characteristics (Table 3) especially the diminished spontaneous and induced cell motility of neutrophils and their reduction of phagocytosis-associated and cyanide-insensitive extra-respiration. The latter phenomenon indicates the impaired (G6P-dependent) metabolic burst [26]. This could be thought to be the expression of a diminished particle-ingestion rate. However, phagocytic ingestion appeared to be normal in case No. 25 [1] and in the recent studies of Seger et al. [51] and Gahr and Heyne [22]. These studies also confirm the (oxidative) killing defect of phagocytes and the suspected impairment of the G6P-dependent hexosemonophosphate (HMP)-shunt activity. A substrate (G6P) limitation of the HMP-shunt is not easy to understand since the formation of G6P as well as the enzymes of the HMP-shunt are localized in the cytosol without membraneous compartmentation.

Further investigations are needed to establish the relationship between the bone marrow maturation arrest, the neutrophil dysfunction and the participation ot the G6P-translocase defect [34].

Table 2. Bone marrow examinations in GSD Ib

'Maturation arrest'	Ragab et al. 1974 [46]
'Maturation arrest, with toxic granulations	Bührdel et al. 1977 [11]
'Normal'	Beaudet et al. 1980 [8]
Maturation arrest (normal up to the band stage)	Mc Cabe et al. 1980 [38]
Moderate myeloid hyperplasia (myeloid: erythroid 4 : 1) without ultrastructural cytologic abnormalities	Anderson et al. 1981 [1]
Maturation arrest of myelopoisis (predominance of promyelocytes with large granules)	Bartram et al. 1981 [6]
'Normal, except for fatty infiltration'	Skaug et al. 1981 [55]
'Mild granulocytic hyperplasia with no maturation arrest'	Roe 1981 [47]

Biochemical characteristics

In 1977 Bialek et al. [9] reported measurement of glucose-6-phosphatase in the presence and absence of the detergent deoxycholic acid (DOC) from the liver of two patients with GSD Ib and four controls. Unfortunately it was not recorded whether the liver sample was fresh or frozen. The hydrolytic activity found in the presence of DOC represents the total enzyme and is called intrinsic activity. Enzymatic activity measured without DOC was lower. Latency was defined as the presence of additional enzymatic activity with DOC divided by the total intrinsic activity. In the four control human livers latent activity ranged from 27.8%–43.0%. However, latency in GSD Ib was 71.8%, 66.7%, 67.4% and 69.2% on four separate occasions. These observations were confirmed 1 year later by Narisawa et al. [42]. Their patient (case No. 21) with GSD Ib had normal activity of glucose-6-phosphatase in a liver specimen stored at −25° C after its collection. In a fresh specimen obtained during a surgical operation for mesentericocaval shunt the activity was very low with 0.8 µmol P/g wet weight/min (lowest normal value 2.0 µmol/g/min). If the homogenate prior to assay was treated for 2 h with deoxycholic acid (DOC), enzyme activity increased to 10.2 µmol/g/min indicating a latency of 92.3%. The latent enzyme activity after treatment with detergent and/or sonication and the differences in enzyme activity between fresh and frozen liver samples were demonstrated in following years by several investigators [7, 8, 13, 34, 51, 52, 55]. These observations led to the hypothesis

Table 3. Characterization of neutrophils in GSD Ib

Impairment of functions	Normal results	Authors
Random and directed cell migration (accumulation of cells into skin windows; failure of mobilization in response to endotoxin, epinephrine)		Beaudet et al. 1980 [8]
Phagocytotic extra-respiration (cyanide-insensitive-hexosemonophosphate-shunt-dependent)		Heyne and Gahr 1980 [25, 26]
	NBT-reduction (qualitative), ultrastructure	Heyne 1981 [27]
Random motility, directed migration, reactivity to chemotactic factors (change of configuration, enhanced adherence, redistribution of surface adhesion sites)	Bactericidal activity (Staphylococcus aureus), stimulated chemiluminescence, histochemical reactions (PAS, sudan black, esterases, alk. phosphatase)	Anderson et al. 1981 [1]
Random cell migration, chemotaxis		Bartram et al. 1981 [6]
Random and directed cell migration, bactericidal activity (Staphylococcus aureus), stimulated oxygen consumption (soluble and particulate stimuli),	Rate of phagocytosis (baker's yeast), cell membrane activation (depolarisation)	Seger et al. 1983 [51]
Superoxide anion production oxitation of 1-^{14}C-glucose	Superoxide anion production after homogenization of cells and NADPH-addition	
Bactericidal capacity (Staphylococces aureus) oxidation of 1-^{14}C-glucose, superoxide anion production		Gahr and Heyne 1983 [22]

that the G6P-hydrolytic activity can only operate if the microsomes are disrupted by freezing, detergents or sonication.

The glucose-6-phosphatase system in intact microsomes of liver consists of three different components [3] which are coupled together: (1) a specific glucose-6-phosphate translocase (T_1) which catalyses penetration of the sugar phosphate into the cisternae of the endoplasmic reticulum; (2) a nonspecific phosphotransferase on the inner surface of the membrane which hydrolyses the sugar phosphate, and (3) a phosphate translocase (T_2) which is responsible for the efflux of inorganic phosphate. Glucose penetrates the membrane by simple diffusion.

Since the phosphate translocase (T_2) also mediates penetration of inorganic pyrophosphate into intact microsomes, the two translocases T_1 and T_2 can be distinguished by assay procedures. In isolated microsomes of fresh liver from a type Ib patient Lange et al. [34] could demonstrate higher than normal activity of phosphate translocase (T_2) and normal activity of glucose-6-phosphohydrolase, thus clearly identifying the glucose-6-phosphate translocase (T_1) as the locus of the enzyme defect. The delay in demonstrating this enzyme defect depends on the fact that the integrity of the membrane for the function of glucose-6-phosphatase was recognised only recently [2]. The freezing procedure of liver samples for the assay of glucose-6-phosphatase has led to false results on the microsomal permeablitity barrier for years, although it is well known that many biological membranes do not tolerate freezing procedures in salt solutions.

In a recent publication Kuzuya et al. [33] demonstrated by histochemical methods normal activity of glucose-6-phosphatase in an adult patient with GSD Ib (case No. 35) whereas this enzyme was not detected in GSD Ia.

Genetics and genetic heterogeneity

GSD Ib is probably transmitted autosomal recessively. Out of 43 patients 18 were female and 18 male. In 17 families reported two had a history of consanguinity, in 3/17 one or two siblings died of unknown causes and three affected children were siblings. The disease is found in the following ethnic groups: Caucasian; Ukrainian; French; Italian; Iraqui; German; Japanese; Belgian; Latin-American; Russian; English; Turkisch; Black; Jugoslavian. Out of 43 cases known to the authors only one female adult patient (case No. 35) had a mild symptomatology with no infections, no neutropenia and residual activity of G6P-translocase.

Patients with the clinical picture of GSD type I and glucose-6-phosphatase activity in frozen liver between 0 and 2 µmol/min/g wet weight (lowest normal value) like the case published by Nuki and Parker [45] and many others should be studied thoroughly before classified as GSD type Ib

Therapy

The therapy of GSD Ib corresponds to that of GSD Ia. Frequent daytime carbohydrate-rich meals and nocturnal nasogastric feeding are the most efficient and harmless methods [28]. Growth retardation, hypoglycemia, hyperuricemia, and marked hyperlactacidemia can be corrected whereas mild hyperlactacidemia may be desirable [19]. However, effects on neutropenia were reported not to be obvious. In cases 23, 31 and 32 [38, 47] this kind of dietetic regimen had some influence on the neutrophil leukocyte count and on recurrent infections. In very severe cases a portocaval shunt may be indicated. In cases 21, 26, and 36 such a therapeutic procedure was performed. The reports were controversial. In case 21 [34] the success is unknown because no follow-up was reported. In case 36 [39] neutropenia and recurrent infections did not respond to this procedure. Only in case 26 [16] were the granulocytes normalized and the recurrent infections eliminated. However, a marked hypochromic anemia, probably caused by sequestration of iron in the spleen (not removed during the portocaval shunt) resistent to therapy remained a persistent feature.

Acknowledgement. The skilful secretarial help of Mrs. Marlis Beckmann is gratefully acknowledged.

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Received May 17 / Accepted June 23, 1983