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Hereditary Fructose Intolerance Mimicking a Biochemical Phenotype of Mucolipidosis: A Review of the Literature of Secondary Causes of Lysosomal Enzyme Activity Elevation in Serum

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Abstract

We describe a patient with failure to thrive, hepatomegaly, liver dysfunction, and elevation of multiple plasma lysosomal enzyme activities mimicking mucolipidosis II or III, in whom a diagnosis of hereditary fructose intolerance (HFI) was ultimately obtained. She presented before introduction of solid foods, given her consumption of a fructose-containing infant formula. We present the most extensive panel of lysosomal enzyme activities reported to date in a patient with HFI, and propose that multiple enzyme elevations in plasma, especially when in conjunction with a normal plasma α-mannosidase activity, should elicit a differential diagnosis of HFI. We also performed a review of the literature on the different etiologies of elevated lysosomal enzyme activities in serum or plasma.

Keywords

hereditary fructose intolerance; mucolipidosis; lysosomal enzyme activity; transferrin isoelectric focusing

INTRODUCTION

The elevation of multiple lysosomal enzyme activities in plasma, with severe reduction in fibroblasts and normal activities in leukocytes, is characteristic for mucolipidosis II

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SUPPORTING INFORMATION

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or III. However, the elevation of multiple lysosomal enzyme acitivities in plasma has also been described in other inborn errors of metabolism, such as congenital disorders of glycosylation, galactosemia, and hereditary fructose intolerance (HFI) [Michelakakis et al., 2009]. This occurs either due to mistargeting of enzymes to compartments other than the lysosomes, eventually leading to their secretion outside of the cell, or due to defective reuptake once they are secreted extracellularly [Barone et al., 1998]. In this report, we present the most comprehensive panel of lysosomal enzyme activities to date in a patient with HFI, and propose that the diagnosis of HFI be suspected in patients with multiple elevated plasma enzyme activities, especially when accompanied by normal α-mannosidase activity. We also provide a word of caution for pediatricians who prescribe infant formula containing fructose, as this can unmask a diagnosis of HFI before introduction of solid foods.

MATERIALS AND METHODS

Lysosomal Enzyme Activities

The activities of 10 lysosomal hydrolases were measured in plasma and six were measured in cultured fibroblasts. A fixed volume of plasma or sonicate was incubated with an enzyme-specific 4-methylumbelliferone (4-MU) conjugated substrate for a specified length of time (0.5–24 hr depending on the specific enzyme). The reaction was stopped by adding a high pH buffer and the fluorescence released during the enzymatic reaction was measured by comparison to a 4-MU standard curve using a Shimadzu fluorometer. Enzyme activities were calculated after correction for sample volume and incubation time. Enzyme activities measured in fibroblasts were also corrected for the total protein concentration of the cell lysate (mg protein). Acid sphingomyelinase activity was measured in a dried blood spot using reagents provided by the Centers for Disease Control. Extract from a 3.2 mm punch was incubated with an enzyme-specific substrate for 20 hr at 37°C and the product purified by a series of liquid/liquid and solid phase extractions prior to injection and analysis on a tandem mass spectrometer. The amount of product formed was compared to a standard curve and enzyme activity was corrected for incubation time and the volume of blood present within a 3.2 mm punch from a dried blood spot card.

Measurements of plasma and leukocyte enzyme activities at 8 months were performed at a different institution, as previously described [Wenger and Williams, 1991].

Carbohydrate Deficient Transferrin (CDT)

For the isoelectric focusing, transferrin species of differing sialic acid content within the patient’s plasma were separated according to their total negative charge via isoelectric focusing utilizing a Phast-gel dry isoelectric focusing system. The transferrin protein sialoforms were visualized using goat antiserum to human transferrin combined with Coomassie blue staining.

CDT by nephelometry was measured by using antibodies that recognize transferrin isoforms that lack sialic acid, while at the same time measuring total transferrin. CDT-coated polysterene particles then bind polysterene particles coated with CDT-monoclonal

antibodies. CDT, depending on its concentration, inhibits this binding, thus allowing its determination by nephelometry. CDT is then calculated as a percentage of total transferrin.

Massively Parallel Sequencing

The genomic DNA was prepared for targeted sequencing using the TruSight One library preparation kit (Illumina, San Diego, CA) following the manufacturer's instructions. Following generation of FASTQ files on a NextSeq 500 sequencer (Illumina), the sequence was aligned to the hg19 reference genome using the Burrows-Wheeler Aligner (BWA) version 0.7.7. The Genome Analysis Toolkit (GATK) version 1.6 was used for variant calling, and Omicia Opal 4.8.0 was used for variant annotation.

Sanger Sequencing

The relevant portion of the *ALDOB* gene was PCR-amplified from genomic DNA. Bidirectional sequence data was obtained and compared to the published reference sequence (NM_000035.3).

CLINICAL REPORT

The patient presented to the hospital at 3 months of age with failure to thrive and greasy stools. Both her weight and weight-for-length were below the third centile, while her length was at the 10th centile. Her liver was palpable 3–4 cm below the right costal margin. An abdominal ultrasound revealed a liver size of 9.1 cm, confirming hepatomegaly, as well as increased liver echogenicity. Laboratory results revealed: (i) cholestasis, with a total bilirubin of 1.4 mg/dl (normal: <0.8), conjugated bilirubin of 1.3 mg/dl (normal: <0.4), and alkaline phosphatase of 707 U/L (normal: 125–547); (ii) hepatocellular damage, with an ALT of 245 U/L (normal: 26–61) and AST of 400 U/L (normal: 16–61); (iii) coagulopathy, with an aPTT of 53.6 sec (normal: 20.8–34.0), PT of 26.1 sec (normal: 11.4–14.0), INR of 2.52 (normal: 0.88–1.14), and fibrinogen of 159 mg/dl (normal: 200–500 mg/dl); (iv) very low HDL level of 3 mg/dl (normal: 12–60); (v) urine analysis without proteinuria or glucosuria, with negative urine reducing substances; (vi) qualitative fecal fat analysis grossly abnormal with large fat globules, 9–75 microns in diameter, so numerous that there was very little fecal background observed microscopically under high power.

Given the presence of hepatomegaly with low HDL levels, the diagnoses of Gaucher and Niemann–Pick type A or B were entertained. Leukocyte β-glucosidase activity was normal at 3.58 nmol/hr/mg (normal: 1.44–14.7), while acid sphingomyelinase activity in a dried blood spot (DBS) was elevated to the degree observed in patients with Mucolipidosis II or III. Additional lysosomal enzyme testing in plasma was found to be suggestive of mucolipidosis (Table I). Subsequent sequencing and deletion/duplication analysis of the *GNTPAB* and *GNTBG* genes did not reveal any pathogenic alterations. Repeat testing of plasma lysosomal enzymes at 7 months of age revealed persistent elevations albeit to a milder degree (Table I).

At follow-up at 8 months, the patient still had profound failure to thrive, by now with a cachectic appearance and prominence of the veins throughout. Both her weight and length were below the third centile, with her weight being average for a 2-month-old girl, and her

length average for a 3-month-old girl. She continued to have liver dysfunction, with an AST of 367 U/L, and ALT of 208 U/L. At this point, lysosomal enzyme activities were measured in plasma, leukocytes, and fibroblasts. Leukocyte and fibroblast activities were essentially normal and only one of the three plasma enzymes measured was elevated (Table II).

At 10 months of age, her uric acid was at the upper limit of normal at 5.3 mg/dl (normal: 1.5–5.4), her serum was noticed to be lipemic, with triglycerides elevated at 345 mg/dl (normal: 33–115), without hypercholesterolemia (total cholesterol 83 mg/dl; normal: 125–170). There was some proximal renal tubular involvement, with hyperphosphaturia (phosphate/creatinine ratio 5.52 mg/mg; normal: 0.34–5.24), but there was no hyperaminoaciduria. Further workup for secondary causes of lysosomal enzyme mistargeting, including congenital disorders of glycosylation (CDGs) or HFI, was pursued. CDT measured by nephelometry was markedly increased at 20.8% (normal: <2.5%), and a transferrin isoelectric focusing (TIEF) run on a stored plasma sample obtained when the patient was 7 months old revealed a type I CDG pattern (see Fig. 1). At this point, further questioning revealed an incipient dietary history of fruit aversion now that she had recently started consuming solid foods.

Subsequent massively parallel sequencing revealed a homozygous mutation in the *ALDOB* gene: c.448G>C (p.Ala150Pro) (dbSNP ID: rs1800546), the most common mutation found in patients with HFI. Targeted Sanger sequencing confirmed the variant identified.

In retrospect, her admission to the hospital occurred 6 weeks after she was weaned. Initially she was placed on Similac® Soy Isomil® (carbohydrate source: corn syrup and sucrose) which likely led to her hospitalization. She was then placed on Similac Expert Care® Alimentum (carbohydrate source: sucrose ± modified tapioca starch ± maltodextrin) and had some improvement of symptoms. Once fructose restriction was initiated at 10 months, there was marked improvement in growth parameters; additionally, the CDT test normalized (not shown).

DISCUSSION

There were several factors that delayed the diagnosis of HFI in our patient. First, it is poorly recognized that several infant milk formulas contain fructose, a fact that can be easily missed and thus impact the speed with which diagnosis is achieved. Other notable findings that delayed diagnosis were the lack of emesis and the fact that she had no urine reducing substances, even in the acute setting. However, this test is known to have poor sensitivity, as it was only positive in 14 of 20 untreated HFI patients tested in one series [Baerlocher et al., 1978], and in 19 of 55 individuals in another [Odièvre et al., 1978]. She also lacked hyperaminoaciduria. On the other hand, an important diagnostic clue was the finding of lipemic serum, as lipemia and hypertriglyceridemia have been described in several patients with HFI [Odièvre, 1969; Borrone et al., 1982]. Finally, the finding of elevated serum lysosomal enzyme activities early in the course of her disease, although previously described in patients with HFI, also contributed to the diagnostic delay since the previously reported elevations were much milder—β-hexosaminidase as high as 1.5 times the upper limit of normal [Michelakakis et al., 2009; Moraitou et al., 2012] compared to 5.1 times

the upper limit of normal in our patient. There are several etiologies for the elevation of multiple lysosomal enzyme activities in serum or plasma (Table III). However, in most of these conditions the increased activities are not within levels compatible with mucolipidosis II or III, as it was in our patient.

An elevation of arylsulfatase A serum activity to about twice the upper limit of normal (ULN) was reported in the first case report of a CDG [Jaeken et al., 1980]. Since then, there have been a few case series reporting elevation of multiple serum lysosomal enzyme activities in patients with a type I CDG pattern [Barone et al., 1998; Beccari et al., 2000], but in all cases where α-mannosidase activity was measured, it was found to be normal. The elevation of multiple lysosomal enzyme activities in serum has also been described in a case of type II CDG, that being COG7-CDG—formerly named CDG-IIe [Spaapen et al., 2005]. These abnormal lysosomal enzyme activities have been hypothesized to result from missorting, reduced intracellular reuptake, and/or decreased enzymatic stability due to defective glycosylation [Barone et al., 1998].

HFI can also cause a positive CDT test as the activity of phosphomannose isomerase is inhibited by accumulated fructose 1-phosphate [Jaeken et al., 1996]. Thus, it is not surprising that increased serum activities of different lysosomal enzymes can exist in cases of secondary disorders of glycosylation such as HFI. Michelakakis et al. [2009] and Moraitou et al. [2012] reported normal activity of plasma α-mannosidase with variable elevations of aspartylglucosaminidase and β-hexosaminidase activities in two patients with HFI, with a decrease of those activities after initiation of fructose restriction. In these prior case reports, however, the degree of elevation was not as pronounced as that seen in mucolipidosis II or III, and thus not as pronounced as in our patient. Of note, plasma lysosomal enzyme activities decreased in our patient before the correct diagnosis was made, as she started self-restricting fructose. As in our patient, plasma lysosomal enzymes have been noted to normalize even with partial fructose restriction, while TIEF still remains abnormal [Moraitou et al., 2012]. TIEF is thus a more sensitive test than lysosomal enzyme analysis for monitoring dietary compliance in HFI. In fact, even in HFI patients on long-term dietary treatment, only 30 of 134 CDT values were found to be normal [Pronicka et al., 2007].

In patients with mucolipidosis type II or III, the activity of lysosomal enzymes in leukocytes is not different than in controls. However, in patients with PMM2-CDG it has been demonstrated that the activities of several lysosomal enzyme activities are reduced in leukocytes [Barone et al., 1998]. In contrast, in a patient with COG7-CDG, several activities were found to be selectively elevated in leukocytes, and decreased in fibroblasts [Spaapen et al., 2005]. Thus, whatever the mechanism by which abnormal glycosylation affects lysosomal enzyme activities in different cell populations, it seems to be different than in mucolipidosis.

In summary, HFI should be included in the differential diagnosis of marked elevation of multiple serum lysosomal enzyme activities, in particular when there is normal activity of α-mannosidase. Clinicians should also be aware that several infant formulas contain fructose.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

Apostolov I, Ivanov E, Adjarov D. 1976. Serum beta-N-acetylglucosaminidase in patients with symptomatic porphyria. Enzyme 21:289–295. [PubMed: 939221]

Baerlocher K, Gitzelmann R, Steinmann B, Gitzelmann-Cumarasamy N. 1978. Hereditary fructose intolerance in early childhood: A major diagnostic challenge. Survey of 20 symptomatic cases. Helv Paediatr Acta 33:465–487. [PubMed: 738900]

Barone R, Carchon H, Jansen E, Pavone L, Fiumara A, Bosshard NU, Gitzelmann R, Jaeken J. 1998. Lysosomal enzyme activities in serum and leukocytes from patients with carbohydrate-deficient glycoprotein syndrome type IA (phosphomannomutase deficiency). J Inherit Metab Dis 21:167–172. [PubMed: 9584269]

Beccari T, Mancuso F, Costanzi E, Tassi C, Barone R, Fiumara A, Orlacchio A, Aisa MC, Orlacchio A. 2000. Beta-hexosaminidase, alpha-D-mannosidase, and beta-mannosidase expression in serum from patients with carbohydrate-deficient glycoprotein syndrome type I. Clin Chim Acta 302:125–132. [PubMed: 11074069]

Begum A, Ittyerah TR. 1970. Arysulfatase and beta-glucuronidase activity in serum in kwashiorkor. Clin Chim Acta 28:263–268. [PubMed: 5447403]

Bernard M, Brochet C, Percheron F. 1985. Decreased serum beta-D-mannosidase activity in diabetic patients, in comparison with other glycosidases. Clin Chim Acta 152:171–174. [PubMed: 4053398]

Borrone C, Lamedica G, Di Rocco M, Canini S, Zanelli C. 1982. [Clinical heterogeneity in fructose intolerance]. Pediatr Medica E Chir Med Surg Pediatr 4:195–202.

Briggs MH, Briggs M. 1975. Serum activity of lysosomal enzymes in relationship to contraceptive steroid dose. Curr Med Res Opin 3:203–205. [PubMed: 1149488]

Calvo P, Barba JL, Cabezas JA. 1982. Serum beta-N-acetylglucosaminidase, beta-D-glucosidase, alpha-D-glucosidase, beta-D-fucosidase, alpha-L-fucosidase and beta-D-galactosidase levels in acute viral hepatitis, pancreatitis, myocardial infarction and breast cancer. Clin Chim Acta 119:15–19. [PubMed: 6800674]

Chitayat D, Nakagawa S, Marion RW, Sachs GS, Shinnar S, Llena JF, Nitowsky HM. 1987. Elevation of serum beta-hexosaminidase and alpha-D-mannosidase in type 2 Gaucher disease: A clinical and biochemical study. J Inherit Metab Dis 10:111–114. [PubMed: 2958659]

Costanzi E, Beccari T, Francisci D, Orlacchio A, Tassi C. 1996. Lysosomal hydrolases in serum from human immunodeficiency virus-infected patients. Clin Chim Acta 255:57–65. [PubMed: 8930413]

Fawzy Montaser M, Amin Sakr M, Omar Khalifa M. 2012. Alpha-L-fucosidase as a tumour marker of hepatocellular carcinoma. Arab J Gastroenterol 13:9–13. [PubMed: 22560818]

Gatsing D, Garba HI, Aliyu R, Adebayo HA, Obekpa P, Adoga IG. 2007. Some lysosomal enzyme profiles in children with nephroblastoma: The effect of nephrectomy. Trends Med Res 2:51–56.

Geokas MC, Rinderknecht H. 1973. Plasma arylsulfatase and beta-glucuronidase in acute alcoholism. Clin Chim Acta 46:27–32. [PubMed: 4732886]

Goi G, Fabi A, Lorenzi R, Lombardo A, Tettamanti G, Burlina AB, Pinelli L, Gaburro D. 1986. Serum enzymes of lysosomal origin as indicators of the metabolic control in diabetes: Comparison with glycated hemoglobin and albumin. Acta Diabetol Lat 23:117–125. [PubMed: 3751446]

Goi G, Lombardo A, Fabi A, Burlina AB, Segalini G, Guagnellini E, Tettamanti G. 1987. Serum enzymes of lysosomal origin as indicators of the metabolic control in non-insulin-dependent diabetics. Acta Diabetol Lat 24:331–340. [PubMed: 3125710]

Gordon BA, Feleki V. 1970. Acid hydrolases in the serum and liver in mucopolysaccharidoses types I and 3. Clin Biochem 3:193–202. [PubMed: 4258597]

Guillou H, David V, Lorcy Y, Le Treut A, Allannic H, Le Gall JY. 1982. Serum lysosomal acid hydrolase activities in Graves' disease. Clin Chim Acta 120:219–224. [PubMed: 6802524]

Hultberg B, Ceder O, Kollberg H. 1981. Acid hydrolases in sera and plasma from patients with cystic fibrosis. Clin Chim Acta 112:167–175. [PubMed: 6263520]

Hultberg B, Isaksson A, Sjöblad S, Ockerman PA. 1980. Acid hydrolases in serum from patients with lysosomal disorders. Clin Chim Acta 100:33–38. [PubMed: 6766092]

Isaksson A, Blanche C, Hultberg B, Joelsson B. 1985. Influence of ethanol on the human serum level of beta-hexosaminidase. Enzyme 33:162–166. [PubMed: 2932329]

Isaksson A, Gustavii B, Hultberg B, Masson P. 1984. Activity of lysosomal hydrolases in plasma at term and post partum. Enzyme 31:229–233. [PubMed: 6236075]

Jaeken J, Kint J, Spaapen L. 1992. Serum lysosomal enzyme abnormalities in galactosaemia. Lancet 340:1472–1473.

Jaeken J, Pirard M, Adamowicz M, Pronicka E, van Schaftingen E. 1996. Inhibition of phosphomannose isomerase by fructose 1-phosphate: An explanation for defective N-glycosylation in hereditary fructose intolerance. Pediatr Res 40:764–766. [PubMed: 8910943]

Jaeken J, Vanderschueren-Lodeweyckx M, Casaer P, Snoeck L, Corbeel L, Eggermont E, Eeckels R. 1980. Familial psychomotor retardation with markedly fluctuating serum prolactin, FSH and GH levels, partial TBG-deficiency, increased serum arylsulphatase A and increased CSF protein: A new syndrome?: 90. Pediatr Res 14:179–179.

Kärkkäinen P, Poikolainen K, Salaspuro M. 1990. Serum beta-hexosaminidase as a marker of heavy drinking. Alcohol Clin Exp Res 14:187–190. [PubMed: 1972003]

Komosińska-Vassev K, Olczyk K, Koźma EM, Winsz-Szczotka K, Olczyk P, Wisowski G. 2003. Graves' disease-associated changes in the serum lysosomal glycosidases activity and the glycosaminoglycan content. Clin Chim Acta 331:97–102. [PubMed: 12691869]

Koskinen H, Järvisalo J, Pitkänen E, Mutanen P, Zitting A. 1984. Serum beta-N-acetylglucosaminidase and beta-glucuronidase activities in silicosis patients and in workers exposed to silica dust. Br J Dis Chest 78:217–224. [PubMed: 6331485]

Krall EA, Basu A, Gloninger MF, Glew RH, Humphries L. 1988. Serum lysosomal hydrolases in cystic fibrosis. Clin Chim Acta 175:1–9. [PubMed: 3168278]

Lügering N, Stoll R, Siekmann A, Faulhaber J, Heese C, Dietrich O, Kucharzik T, Busch H, Hasilik A, Domschke W. 1995. Elevated levels of activities of beta-hexosaminidase and alpha-mannosidase in human immunodeficiency virus-infected patients. J Infect Dis 171:683–686. [PubMed: 7876617]

Michelakakis H, Moraitou M, Mavridou I, Dimitriou E. 2009. Plasma lysosomal enzyme activities in congenital disorders of glycosylation, galactosemia and fructosemia. Clin Chim Acta 401:81–83. [PubMed: 19100247]

Moffitt KD, Chambers JP, Diven WF, Glew RH, Wenger DA, Farrell DF. 1978. Characterization of lysosomal hydrolases that are elevated in Gaucher's disease. Arch Biochem Biophys 190:247–260. [PubMed: 101149]

Moraitou M, Dimitriou E, Mavridou I, Michelakakis H, Georgouli H, Ploski R, Pollak A. 2012. Transferrin isoelectric focusing and plasma lysosomal enzyme activities in the diagnosis and follow-up of hereditary fructose intolerance. Clin Chim 413:1714–1715.

Nagasue N, Inokuchi K, Kanashima R. 1982. Serum activities of lysosomal enzymes in patients with liver cell carcinoma. Dig Dis Sci 27:454–458. [PubMed: 6176411]

Nakagawa S, Kumin S, Sachs G, Nitowsky HM. 1983. Changes of serum hexosaminidase for the presumptive diagnosis of type I Gaucher disease in Tay-Sachs carrier screening. Am J Med Genet 14:525–532. [PubMed: 6859103]

Ockerman PA. 1968a. Acid hydrolases in skin and plasma in gargoylism. Deficiency of beta-galactosidase in skin. Clin Chim Acta 20:1–6. [PubMed: 4967992]

Ockerman PA. 1968b. Lysosomal enzymes in juvenile amaurotic idiocy. Acta Paediatr Scand 57:537–539. [PubMed: 5706371]

Ockerman PA, Kohlin P. 1969. Acid hydrolases in plasma in Gaucher's disease. Clin Chem 15:61–64. [PubMed: 4884797]

Odièvre M 1969. [Diagnostic problems of hereditary intolerance to fructose in young infants]. Arch Fr Pédiatrie 26:5–19.

Odièvre M, Gentil C, Gautier M, Alagille D. 1978. Hereditary fructose intolerance in childhood. Diagnosis, management, and course in 55 patients. Am J Dis Child 1960:605–608.

Omene JA, Adamson I, Okolo AA, Glew RH. 1979. Changes in serum lysosomal hydrolases in marasmus. Clin Chim Acta 91:213–219. [PubMed: 103662]

Perry W, Jenkins MV, Erooga MA, Stamp TC. 1978. Elevation of plasma levels of lysosomal enzymes during treatment with rifampicin and isoniazid. Biochem Med 20:153–159. [PubMed: 32879]

Pronicka E, Adamowicz M, Kowalik A, Płoski R, Radomyska B, Rogaszewska M, Rokicki D, Sykut-Cegielska J. 2007. Elevated carbohydrate-deficient transferrin (CDT) and its normalization on dietary treatment as a useful biochemical test for hereditary fructose intolerance and galactosemia. Pediatr Res 62:101–105. [PubMed: 17515832]

Reglero A, Carretero MI, Cabezas JA. 1980. Increased serum alpha-L-fucosidase and beta-N-acetylglucosaminidase activities in diabetic, cirrhotic and gastric cancer patients. Clin Chim Acta 103:155–158. [PubMed: 6245816]

Saha AK, Glew RH, Kotler DP, Omene JA. 1991. Elevated serum beta-glucuronidase activity in acquired immunodeficiency syndrome. Clin Chim Acta 199:311–316. [PubMed: 1663007]

Spaapen LJM, Bakker JA, van der Meer SB, Sijstermans HJ, Steet RA, Wevers RA, Jaeken J. 2005. Clinical and biochemical presentation of siblings with COG-7 deficiency, a lethal multiple O- and N-glycosylation disorder. J Inherit Metab Dis 28:707–714. [PubMed: 16151902]

Stibler H, Jaeken J, Kristiansson B. 1991. Biochemical characteristics and diagnosis of the carbohydrate-deficient Glycoprotein syndrome. Acta Pædiatrica 80:21–31.

Takahashi H, Saibara T, Iwamura S, Tomita A, Maeda T, Onishi S, Yamamoto Y, Enzan H. 1994. Serum alpha-L-fucosidase activity and tumor size in hepatocellular carcinoma. Hepatol 19:1414–1417.

Ungewickell AJ, Majerus PW. 1999. Increased levels of plasma lysosomal enzymes in patients with Lowe syndrome. Proc Natl Acad Sci 96:13342–13344. [PubMed: 10557322]

Vaysse J, Pilardeau P, Gattegno L. 1990. Variations in serum alpha-L-fucosidase activity during childhood and pregnancy. Clin Chim Acta 187:273–280. [PubMed: 2323066]

Waters PJ, Flynn MD, Corrall RJ, Pennock CA. 1992. Increases in plasma lysosomal enzymes in type 1 (insulin-dependent) diabetes mellitus: Relationship to diabetic complications and glycaemic control. Diabetologia 35:991–995. [PubMed: 1451959]

Wenger DA, Williams C. 1991. Techniques in diagnostic human biochemical genetics: A laboratory manual. In: Hommes F, editor. Screening for lysosomal disorders. New York: Wiley-Liss. pp 587–617.

Woollen JW, Turner P. 1965. Plasma N-acetyl-beta-glucosaminidase and beta-glucuronidase in health and disease. Clin Chim Acta 12:671–683. [PubMed: 5880048]

Woźniak A, Drewa T, Rozwodowska M, Drewa G, Lambrecht W, Wiśniewska I. 2002. Activity of some lysosomal enzymes in serum and in tumors of patients with squamous cell lung carcinoma. Neo-plasma 49:10–15.

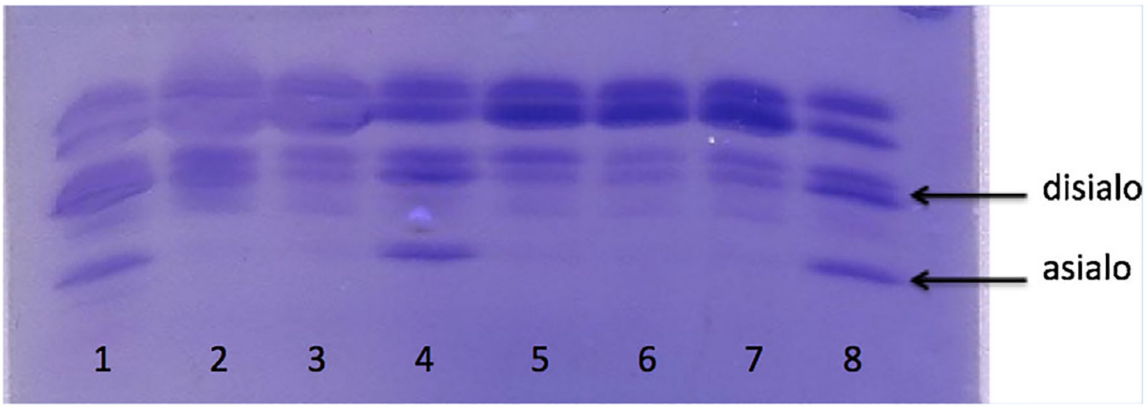

FIG. 1.

Transferrin isoelectric focusing at 7 months. Lane 1: PMM2-CDG positive control; lane 2: negative control; lanes 4 and 8: patient.

Table I.

Lysosomal Enzyme Activities in Plasma*

Enzyme	At 3 months (× ULN)	At 7 months (× ULN)	Normal range	Mucolipidosis range
α-fucosidase	**1,894 (2.5×)**	**1,741 (2.3×)**	50–743	850–3,361
β-glucuronidase	*154* (*1.4×*)	86	5–111	350–1,358
β-hexosaminidase	**8,037 (5.1×)**	*1,935* (*1.2×*)	250–1,568	6,276–20,093
α-mannosidase	39	47	20–54	842–3,285
β-mannosidase	**1,035 (5.7×)**	558 (3.1×)	50–181	707–2,204
α-iduronidase	1.6	**46.72 (3.6×)**	3–13	34–400
Iduronate-2-sulfatase	587.9	707.4	155–1,082	3,632–6,272
α-N-acetylgalactosaminidase		*502* (*1.9×*)	39–264	1,595–4,931
α-N-acetylglucosaminidase		274.3	97–1,064	1,301–1,739
α-galactosidase		1.94	0.52–2.8	5–18.9
Acid sphingomyelinase (DBS)	**70.7 (3.2×)**	**63.6 (2.9×)**	1.63–22.1	45.8–302

Numbers in bold are within the ML range and those in italics are elevated, but below the ML range.

*Units of measurement: Iduronate-2-sulfatase: nmol/4 hr/ml; α-N-acetylglucosaminidase: nmol/17 hr/ml; all others: nmol/hr/ml.

Table II.

Lysosomal Enzyme Activities at 8 Months

Plasma			
Enzyme	**Activity (nmol/h/ml)**	**Normal control range**	**Mucolipidosis range[a]**
β-galactosidase	**95.5**	5–60	91–586
α-N-acetylglucosaminidase	26.3	8.6–104	116–400
β-Hexosaminidase total	1,200	113–1,500	3,400–10,800

Leukocytes		
Enzyme	**Activity (nmol/h/mg)**	**Normal control range**
β-galactosidase	72.5	50–120
β-mannosidase	67.3	60–130
β-Hexosaminidase A	155.3	145–275
Arylsulfatase A	57.0	45–80
Galactocerebrosidase	2.4	0.8–4.5
Sphingomyelinase	2.9	0.5–3.5
Glucocerebrosidase	4.0	2.8–12.0
Acid lipase	345.2	110–500
Fibroblasts		
Enzyme	**Activity (nmol/hr/mg)**	**Normal control range**
α-fucosidase	24.8	12.3–130.7
α-iduronidase	27.4	25.4–222.6
α-N-acetylgalactosaminidase	23.4	12.6–94
β-glucosidase	100.0	13.2–314.2
β-galactosidase	424.2	149–608
Sialidase	21.9	23–74

Numbers in bold are within the ML range.

[*] Mucolipidosis range is different than in Table I since the test was obtained at a different institution.

Table III.

Review of the Literature on Conditions Associated With Secondary Elevation of Lysosomal Enzyme Activity in Serum or Plasma

Condition	Enzyme	Increased activity compared to controls[a]	Activity similar to controls	Proposed mechanism	References
CDG type I	β-gal	1.9×	Sia,	Missorting, reduced intracellular reuptake, and/or decreased enzymatic stability due to defective glycosylation	Stibler et al. [1991]
	NAGLU	2.5×	α-man		
	ARS A	1.8×	α-fuc,		Barone et al. [1998]
	β-hex	1.9×	α-NAGLU,		
	β-gal	2.0×	β-man		
	β-glu	4.2×			
	Total	1.9×	α-man		Beccari et al.
	β-hex				[2000]
	β-man	5×			
	AGA	2–6× ULN	α-man,		Michelakakis
	β-hex	1.4–3× ULN	β-man		et al. [2009]
COG7-CDG	ARS A	10.2× ULN	-	Abnormal enzymatic glycosylation; not explained by altered biosynthesis of M6P residues or altered localization of the CI-MPR	Spaapen et al. [2005]
	α-fuc	4.2× ULN			
	β-gal	7.8× ULN			
	Total	3.3× ULN			
	β-hex				
	β-hex A	3.3× ULN			
	β-glu	4.9× ULN			
	α-man	3.2× ULN			
Galactosemia (untreated)	β-hex	2.0–3.8× ULN	α-fuc	Abnormal glycosylation of enzymes	Jaeken et al. [1992]
	AGA	2.5–4.6× ULN	α-man		Michelakakis
	β-man	Up to 1.8× ULN			et al. [2009]
	β-hex	1.8–2.6× ULN			
Hereditary fructose intolerance	AGA	2.6–4.3× ULN	α-man	Abnormal glycosylation of enzymes	Michelakakis et al. [2009]

Condition		Enzyme	Increased activity compared to controls[a]	Activity similar to controls	Proposed mechanism	References
		β-hex	Up to 1.5× ULN			
		AGA	2.2–2.6× ULN	α-man,		Moraitou et al. [2012]
		β-hex	Up to 1.5× ULN	β-man		
Diabetes mellitus		α-fuc	5.0×	α-man,	Non-enzymatic glycation of enzymes?	Reglero et al. [1980]
				α-gal,		
				β-gal		
	Type 1	β-glu[b]	1.4×	α-fuc,		Waters et al. [1992]
		α-man	1.6×	β-gal,		
				β-man		
		β-hex[b]	Up to 1.3×	–		Goi et al. [1986]
		β-glu[b]	Up to 1.7×			
		β-gal	Up to 1.3×			
		α-gal	Up to 1.4×			
		α-fuc	Up to 1.5×			
		α-glc	Up to 1.3×			
		β-glc	Up to 1.7×			
		α-man	Up to 1.4×			
		α-fuc	1.5×	β-man		Bernard et al. [1985]
	Type 2	α-fuc	1.4×	decreased		
		β-glu	1.4×	β-gal,		Goi et al. [1987]
		α-man	1.3×	α-fuc,		
				α-glc and β-glc		
Alcohol use		β-hex	2.5×	α-fuc	Liver damage and/or increased permeability of lysosomal membrane	Isaksson et al. [1985]
		α-man	1.7×			
		β-hex	2.1×	–		Kärkkäinen et al. [1990]
		β-glu	4.6×	–		Geokas and Rinderknecht [1973]
		ARS	2.4×			
Lowe syndrome		β-glu	1.6×	α-NAGLU	Abnormal enzyme trafficking due to accumulation of lysosomal	Ungewickell and Majerus [1999]

Condition		Enzyme	Increased activity compared to controls[a]	Activity similar to controls	Proposed mechanism	References
					phosphatidylinositol 4,5-bisphosphate impairing formation of clathrin-coated vesicles	
		α-fuc	2.0×			
		α-man	1.7×			
		β-hex	2.0×			
		β-gal	1.9×			
		α-gal	1.6×			
Gaucher disease		β-gal	1.9×	α-man	Increased lysosomal membrane permeability?	Ockerman and Kohlin [1969]
		β-hex	2.6×			
		β-glu	3.1×			
		α-fuc	1.6×			
		β-hex (mainly B)	1.8×	–		Moffitt et al. [1978]
		β-hex (mainly B)	3.1×	–		Nakagawa et al. [1983]
		β-hex	1.6× ULN	α-man,		Hultberg et al. [1980]
		β-glu	1.5×	α-fuc, β-glc		
	Type 2	Total hex	42.3×	–		Chitayat et al. [1987]
		α-man	48.8×			
MPS		β-gal	2.5×	α-fuc	Increased lysosomal membrane permeability?	Ockerman 1968a
		β-glu	5.6×			
		β-hex	2.8×			
	MPS I	β-hex	1.3× ULN	α-man,		Hultberg et al. [1980]
		β-glu	1.6× ULN	α-fuc, β-glc		
		β-glu	3.2×	–		Gordon and Feleki [1970]
		β-hex	2.6×			

Condition		Enzyme	Increased activity compared to controls[a]	Activity similar to controls	Proposed mechanism	References
		ARSA	3.4×			
	MPS II	β-hex	1.3× ULN	α-man,		Hultberg et al. [1980]
		β-glu	1.9× ULN	α-fuc,		
				β-glc		
	MPS III	β-glu	1.3× ULN	α-man,		Hultberg et al. [1980]
				α-fuc,		
				β-glc		
		β-glu	5.2×	–		Gordon and Feleki [1970]
		β-hex	3.6×			
		ARS A	3.9×			
Metachromatic leukodystrophy		β-glu	1.3× ULN	α-man,	Increased lysosomal membrane permeability?	Hultberg et al. [1980]
				α-fuc,		
				β-glc		
Tay-Sachs disease		β-glu	1.7× ULN	α-man,	Increased lysosomal membrane permeability?	Hultberg et al. [1980]
				α-fuc,		
				β-glc		
		β-gal	1.5×	β-hex.		Ockerman [1968b]
		β-glu	3.8×	α-man was decreased		
		α-fuc	1.8×			
Liver disease	Acute viral hepatitis	β-hex	2.2×	β-gal	Release from damaged hepatocytes or Kupfer cells and/or decreased clearance from circulation	Calvo et al. [1982]
		β-glc	1.9×			
		α-glc	2.0×			
		α-fuc	2.0×			
	Liver cirrhosis	β-glu	1.8×	–		Nagasue et al. [1982]
		α-fuc	1.9×	–		Takahashi et al. [1994]

Condition		Enzyme	Increased activity compared to controls[a]	Activity similar to controls	Proposed mechanism	References
		α-fuc	5.8×	α-man		Reglero et al. [1980]
		α-gal	1.4×			
		β-gal	1.5×			
		β-hex	1.6×			
		β-glu	1.4×			
	HCC	β-glu	2.6×[c]	–		Nagasue et al. [1982]
		α-fuc	3.4×	–		Takahashi et al. [1994]
		α-fuc	22.1×			Fawzy Montaser et al. [2012]
Cancer	Gastric cancer	α-fuc	7.0×	α-man,	Cell damage, increased production and/or reduced clearance	Reglero et al. [1980]
		α-gal	1.6×	β-glu		
		β-gal	1.6×			
	Breast cancer	β-hex	1.4×	α-fuc.	Cell damage, increased production and/or reduced clearance	Calvo et al. [1982]
		β-glc	1.5×	β-gal decreased		
	Wilms tumor	β-glu	3.8×	β-gal	Cell damage, increased production and/or reduced clearance	Gatsing et al. [2007]
	Lung cancer	ARS	Up to 5.3×[c]	–	Excessive release from disrupted lysosomes of neoplastic cells and/or increased synthesis by tumor tissue	Woźniak et al. [2002]
Cystic fibrosis		β-hex	1.7×	α-man,	Cell damage	Hultberg et al. [1981]
		β-gal	4.4×	α-fuc		
		α-glc	1.9×			
		α-gal	1.8×			
		β-glu	1.7×			
		β-hex[f]	1.5–2.0×	α-fuc,		Krall et al. [1988]
		α-man[g]	2.0–2.4×	β-glu		
Porphyria cutanea tarda		β-hex	2.1×[d]	–	Accumulation of uroporphyrin in lysosomes leading to lysosomal membrane damage	Apostolov et al. [1976]
Pregnancy		α-fuc	2.3× (at term)	–	Placental origin and/or estrogen induction	Isaksson et al. [1984]

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Condition	Enzyme	Increased activity compared to controls[a]	Activity similar to controls	Proposed mechanism	References
	β-glu	2.3× (at term)			
	β-hex	5.0× (at term)			
	α-man	2.5× (at term)			
	α-fuc	2.3×[e]	–		Vaysse et al. [1990]
	β-hex	8.2×	–		Woollen and Turner [1965]
	β-glu	4.5×			
Oral contraceptives	β-glu	1.3–6.8×[h]	–	Labilisation of lysosomal membranes?	Briggs and Briggs [1975]
Graves disease (untreated)	α-glc	1.3×	β-gal	Increased synthetic rate of lysosomal enzymes?	Guillou et al. [1982]
	β-glu	2.2×			
	Hex	1.6×			
	α-fuc	1.8×			
	α-man	1.5×			
	β-hex	2.5×	α-man		Komosińska-Vassev et al. [2003]
	β-glu	18.0×			
	β-gal	3.0×			
	α-fuc	2.2×			
Myocardial infarction	β-hex	1.3×	α-fuc	Cell damage	Calvo et al. [1982]
	β-glc	1.3×			
	α-glc	1.4×			
Acute pancreatitis	β-hex	1.7×	α-fuc,	Cell damage	Calvo et al. [1982]
	β-glc	1.6×	β-gal		
Silicosis	β-hex	1.4×	β-glu	Activation of pulmonary macrophages	Koskinen et al. [1984]
Malnutrition	β-glu	2.1×	–	Liver dysfunction and/or vitamin A deficiency-induced lysosomal leakage	Begum and Ittyerah [1970]
	β-glu	2.2×	Hex		Omene et al. [1979]
Rifampicin + isoniazid (tuberculosis treatment)	β-glu	3.5×	–	Enzymatic induction	Perry et al. [1978]
	β-hex	1.6×			

Condition	Enzyme	Increased activity compared to controls[a]	Activity similar to controls	Proposed mechanism	References
HIV infection	β-glu	Up to 16.2×[i]	α-man, α-gal, β-gal	Release from HIV-infected leukocytes	Saha et al. [1991]
	α-man	Up to 3.4×[c]	β-glu, β-gal		Lügering et al. [1995]
	β-hex	Up to 2.9×[c]			
	β-hex	1.4×	β-hex A, β-glu, β-gal		Costanzi et al. [1996]
	α-man	2.0×			
	β-man	1.9×			

α-fuc, α-fucosidase; α-glc, α-glucosidase; α-man, α-mannosidase; AGA, Aspartylglucosaminidase; ARS, ARS; β-gal, β-galactosidase; β-glc, β-glucosidase; β-glu, β-glucuronidase; β-hex, β-hexosaminidase; β-man, β-mannosidase; CDG, Congenital disorders of glycosylation; CI-MPR, cation-independent mannose 6-phosphate receptor; HCC, Hepatocellular carcinoma; M6P, mannose 6-phosphate; MPS, mucopolysaccharidosis; NAGLU, NAGLU; Sia, Sialidase; ULN, upper limit of normal.

[a] Expressed as mean activity in the disease state divided by mean activity in controls. When the mean activity for controls is not provided, the comparison is made against the upper limit of the normal range. When comparing means, only data that was shown to be statistically significant—with a $P < 0.05$—and increased by at least 25% is included in the table. Numbers are rounded to the nearest decimal.

[b] Correlates with glycemic control.

[c] Increases with stage of disease.

[d] Increases in active stage.

[e] Increases throughout pregnancy.

[f] Increases with severity of pulmonary involvement.

[g] Only in patients >13 years old; increases with severity of pulmonary involvement.

[h] Increase with dose.

[i] Correlates inversely with CD4 count.