Case Report

Fluorodeoxyglucose-positron emission tomography as a potential alternative tool for functional diagnosis of glycogen storage disease type I

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ABSTRACT

A 43-year-old woman with genetically confirmed glycogen storage disease type Ib was suspected to have left breast cancer. Fluorodeoxyglucose-positron emission tomography showed high fluorodeoxyglucose accumulation in the whole liver as well as left mammary gland. We consider that high fluorodeoxyglucose accumulation in the liver of patients with glycogen storage disease type I is caused by impaired glucose-6-phosphate metabolism due to the congenital deficiency of glucose-6-phosphatase activities in hepatocytes. This study describes fluorodeoxyglucose-positron emission tomography as a potential alternative tool to diagnose glycogen storage disease type I functionally.

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Introduction

Glycogen storage disease (GSD) is caused by a defect in an enzyme associated with glycogen metabolism. It is characterized by hypoglycemia and hepatomegaly. The different types of GSD each require specific management. Therefore, we must make stringent efforts to diagnose GSD and determine the type accurately. Due to similar physical presentation and laboratory findings, distinguishing between GSD types is difficult without diagnostic tests. Genetic testing is a powerful tool for

Abbreviations: FDG-PET, Fluorodeoxyglucose-positron emission tomography; GSD, Glycogen storage disease.

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determining GSD types, but it is expensive and can be performed only by a few laboratories. Therefore, many patients with suspected GSD may be waiting for confirmation of their diagnosis and specific type due to lack of available diagnostic tools [1].

GSD type I, caused by the deficiency of glucose-6-phosphatase activities, has 2 subtypes: GSD type Ia and GSD type Ib due to the deficiency of glucose-6-phosphatase catalytic activity and glucose-6-phosphate exchanger SLC37A4 activity, respectively [2]. Genetic testing for the G6PC1 and SLC37A4 genes is a noninvasive tool to diagnose GSD type Ia or GSD type Ib, respectively. However, when genetic testing is inconclusive, liver biopsy is the only available tool for functional diagnosis, and only few laboratories assess hepatic enzyme activities.

Herein, we would like to report an adult patient with GSD type Ib who showed unique observations on fluorodeoxyglucose-positron emission tomography (FDG-PET), and focus on FDG-PET as a potential alternative tool for functional diagnosis of GSD type I.

**Case report**

The proband was a female patient. Since childhood, she exhibited clinical manifestations associated with GSD: recurrent epistaxis and abdominal distention at 4 years of age; recurrent stomatitis at 12 years; pain and swelling in the dorsum of the foot and ankle, resulting in the diagnosis of gout and hyperuricemia at 18 years; hyperlipidemia at 20 years; and fasting hypoglycemia and hyperlactatemia at 25 years. At 26 years of age, she was referred to our hospital, and detailed examinations were performed. Her height was 153.9 cm (−0.8 SD). Physical examinations showed hepatomegaly. Laboratory examination results under allopurinol and simvastatin prescriptions were as follows: white blood cells, 2400/μL (reference, 3500–8500/μL); neutrophils, 280/μL (<1500/μL, defined as neutropenia); aspartate aminotransferase, 19 U/L (reference, 14–32 U/L); alanine aminotransferase, 22 U/L (reference, 8–41 U/L); creatinine, 0.3 mg/dL (reference, 0.4–0.7 mg/dL); uric acid, 7.9 mg/dL (reference, 2.9–5.3 mg/dL); total cholesterol, 199 mg/dL (reference, 140–220 mg/dL); high-density lipoprotein, 51 mg/dL (reference, 50–98 mg/dL); and low-density lipoprotein, 90 mg/dL (reference, 71–140 mg/dL). Oral glucose tolerance test revealed that high lactate level, 38.2 mg/dL (reference, 3.7–16.3 mg/dL), decreased to normal level, 5.2 mg/dL. Imaging studies revealed an 8-mm nodule located in hepatic segment 6. Thus, she was suspected of having GSD type I. After obtaining informed consent, we identified SLC37A4 (NM_001164277.1) p.[Arg166Leu];[Ser172Glyfs*39] via genetic testing, confirming the diagnosis of GSD type Ib [3]. She was instructed to ingest cornstarch in addition to frequent glucose intake to avoid hypoglycemia. At 35 years of age, the size of the previously detected hepatic nodule had increased to 14 mm, and another hepatic nodule, measuring 8 mm, was identified in hepatic segment 7.

At 43 years of age, during a medical checkup, mammography revealed grouped calcification and focal asymmetric density in her left breast. Core needle biopsy revealed no malignant findings. Abdominal ultrasonography showed 2 hepatic nodules, measuring 17 and 13 mm, located in hepatic segments 6 and 7, respectively. At 44 years of age, the breast calcification had increased. High-grade ductal carcinoma-in-situ was suspected following stereotactic mammotome biopsy. A whole-body FDG-PET showed high FDG accumulation in the enlarged liver and left mammary gland (Figs. 1A–C). At 45 years of age, nipple-sparing mastectomy was performed. No metastasis was seen at the sentinel lymph node. Pathologic examination confirmed high grade ductal carcinoma-in-situ. Tamoxifen as an adjuvant chemotherapy was initiated; however, it was discontinued one month later due to development of stomatitis. No recurrence was seen 16 months after the operation.

**Discussion**

In this article, we reported an adult patient with GSD type Ib whose whole liver and the breast cancer showed high FDG accumulation.

This increased FDG accumulation in our patient’s liver was similar to that previously reported in a GSD type Ib patient and GSD type Ia patient [4,5]. FDG-PET localizes tumors by detecting the FDG-6-phosphate accumulation in tumor cells with a deficiency of glucose-6-phosphatase [6]. Considering the mechanism of FDG accumulation in tumor cells, high FDG accumulation in the liver of these GSD type I patients is considered to be caused by impaired glucose-6-phosphate metabolism in hepatocytes. Additionally, FDG accumulation in our patient’s liver may be higher than that reported in the previous GSD type Ib case [4]. We speculate that the degree of FDG accumulation is inversely correlated with the residual activity of SLC37A4 [4]. In our patient, the SLC37A4 p.Arg166Leu variant had low residual activity (3.2%), and the SLC37A4 p.Ser172Glyfs*39 variant was predicted to cause loss of function; no variant information was available for the previous GSD type Ib case [4,7]. Thus, we consider that FDG-PET can be applied for functional diagnosis of GSD type I.

We should recognize the possible risk of radiation exposure to the liver in GSD type I patients more than in non-GSD type I individuals, due to delayed washout of FDG-6-phosphate from hepatocytes with decreased glucose-6-phosphatase activity in GSD type I patients. Furthermore, considering the development of hepatic adenomas and hepatocellular carcinoma in GSD type I patients, radiation exposure may be a concern for tumorigenesis and malignant transformation. Minimizing radiation exposure, including dose reduction, is essential when applying FDG-PET for functional diagnosis of GSD type I.

The utility of FDG-PET in the functional diagnosis of other hepatic GSDs, such as types III, IV, VI, and IX has not been reported. Theoretically, because of intact glucose-6-phosphatase activity, the degree of FDG-6-phosphate accumulation in other hepatic GSDs is speculated to be similar to that in non-GSD individuals. Therefore, we consider that the potential utility of FDG-PET as a tool for functional diagnosis is limited only to GSD type I.

This case demonstrates an important pitfall in the interpretation of FDG-PET for oncology. In our patient, FDG-PET de-
Fig. 1 – Fluorodeoxyglucose-positron emission tomography images of the patient. Increased FDG accumulation in the whole liver (SUVmean: 5.13) (A, B), and the left breast lesion (C), denoted by the white arrow, on a Siemens Biograph 64 Vision 600 PET/CT scanner one hour after an injected activity of 232.7 MBq. Lower and upper window settings were 0 and 6, respectively.

tected the breast lesion but failed to show the liver lesions; thus, the liver metastases could not be evaluated. Despite the utility of whole-body FDG-PET in detecting the primary cancer and metastases, it is not the appropriate modality to evaluate liver lesions in patients with GSD type I.

In conclusion, FDG-PET is an alternative tool for functional diagnosis of GSD type I.

Patient consent

Informed written consent was obtained from the patient for publication of the case report and the imaging studies.

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