Genes & Diseases (2023) 10, 701–704

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.keaipublishing.com/en/journals/genes-diseases

RAPID COMMUNICATION

A patient with glycogen storage disease type IA combined with hepatic adenoma: A case report

Glycogen storage disease (GSD) is a rare autosomal recessive disease by abnormal accumulation of intracellular glycogen.[1] Mutations in genes encoding G-6-P or G-6-Pase lead to dysfunction of the body's glycogen metabolism. Without adequate metabolic treatment, patients with GSD can die during infancy or childhood from severe hypoglycemia and acidosis. The patient's symptoms generally achieve remission during adolescence, except in rare cases when cirrhosis of the liver or myopathy occurs. Once GSD is identified in adults, the patients are often accompanied by many complications, such as fasting hypoglycemia, hyperlipidemia, hyperlactatemia and hyperuricemia. In most cases, these complications may mask the patient's primary disease. At present, there are more than 14 types of GSD. The details were presented in Table S1. It's worth noting that Glycogen storage disease type IA (GSD-IA) is the most prevalent subtype and represents approximately 80% of GSD-I cases. It's characterized by a deficiency of glucose-6 phosphatase (G-6-P), a key enzyme in glycogen metabolism. However, G-6-Pase deficiency blocked the normal pathway of glycogenolysis and glycogen is accumulated excessively in the liver or muscle. This is why the patients with GSD are typically characterized by hypoglycemia and hepatomegaly. Once the metabolic alternative pathways are activated, the body will develop various complications.

To improve the awareness and knowledge of this disease, we report a patient with GSD-IA who was hospitalized in Zhongnan Hospital of Wuhan University in 2019. The detailed patient history is as follows: the patient, a 29-year-old male, was hospitalized due to upper gastrointestinal bleeding on June 17, 2019. After the consultation, we knew the patient had a 5-year history of gout and took nonsteroidal anti-inflammatory drugs (NSAIDs). We suspected that the upper gastrointestinal bleeding was related to the long-term use of NSAIDs. The results of gastroscopy also supported this conclusion (Fig. 1A). After hemostasis under gastroscopy, the patient recovered well. Multiple liver masses were subsequently found by CT examination at admission. The patient underwent percutaneous liver biopsy, and the pathological result was benign liver adenoma. Given that liver adenoma is a benign tumor, surgery was not performed on the patient. The main treatment advice was conservative treatment and regular review. From June 17, 2019 to June 7, 2021, after two years of follow-up, the number and volume of hepatic adenomas increased. The CT and MRI results on June 17, 2019 showed that the largest adenoma was located in the left lobe of the liver, with a size of about 40 * 29 mm. The intrahepatic nodule showed obvious hyperintensity in the arterial phase and portal venous phase. On June 7, 2021, MRI results showed that the tumor in the left outer lobe of the liver was significantly enlarged, with a size of about 59 * 37 mm. The left lateral lobe mass in the arterial phase has nodules, and other parts of the liver have multiple nodular and abnormal enhancement foci (Fig. 1B). To prevent malignant transformation, we performed laparoscopic left liver resection + liver radiofrequency ablation for hepatic adenoma. Preoperative examination showed multiple gout nodules and multiple xanthomas on the back and large joints (Fig. 1C). The results of biochemical examination at admission indicated Glu 3.57 mmol/L (glucose 3.9–6.1 mmol/L), TC 6.65 mmol/L (total cholesterol 5.17–6.45 mmol/L), TG 8.93 mmol/L (triglyceride 1.70–2.30 mmol/L), NEFA 1.1391 mmol/L (free fatty acid 0.3–0.9 mmol/L), ALT 35 U/L (0–40 U/L), AST 48 U/L (0–40 U/L), GGT 231 U/L (glutamyl transpeptidase 3–50 U/L), ALP 28.3 U/L (alkaline phosphatase 40–150 U/L) and UA 559.1 μmol/L (uric acid 237.9–356.9 μmol/L), respectively. The appearance of the specimen was similar to that of hepatic adenoma. The postoperative pathological results supported the diagnosis of multiple hepatic adenomas (Fig. 1D). The results of

Peer review under responsibility of Chongqing Medical University.

https://doi.org/10.1016/j.gendis.2022.08.002

2352-3042/© 2022 The Authors. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co., Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

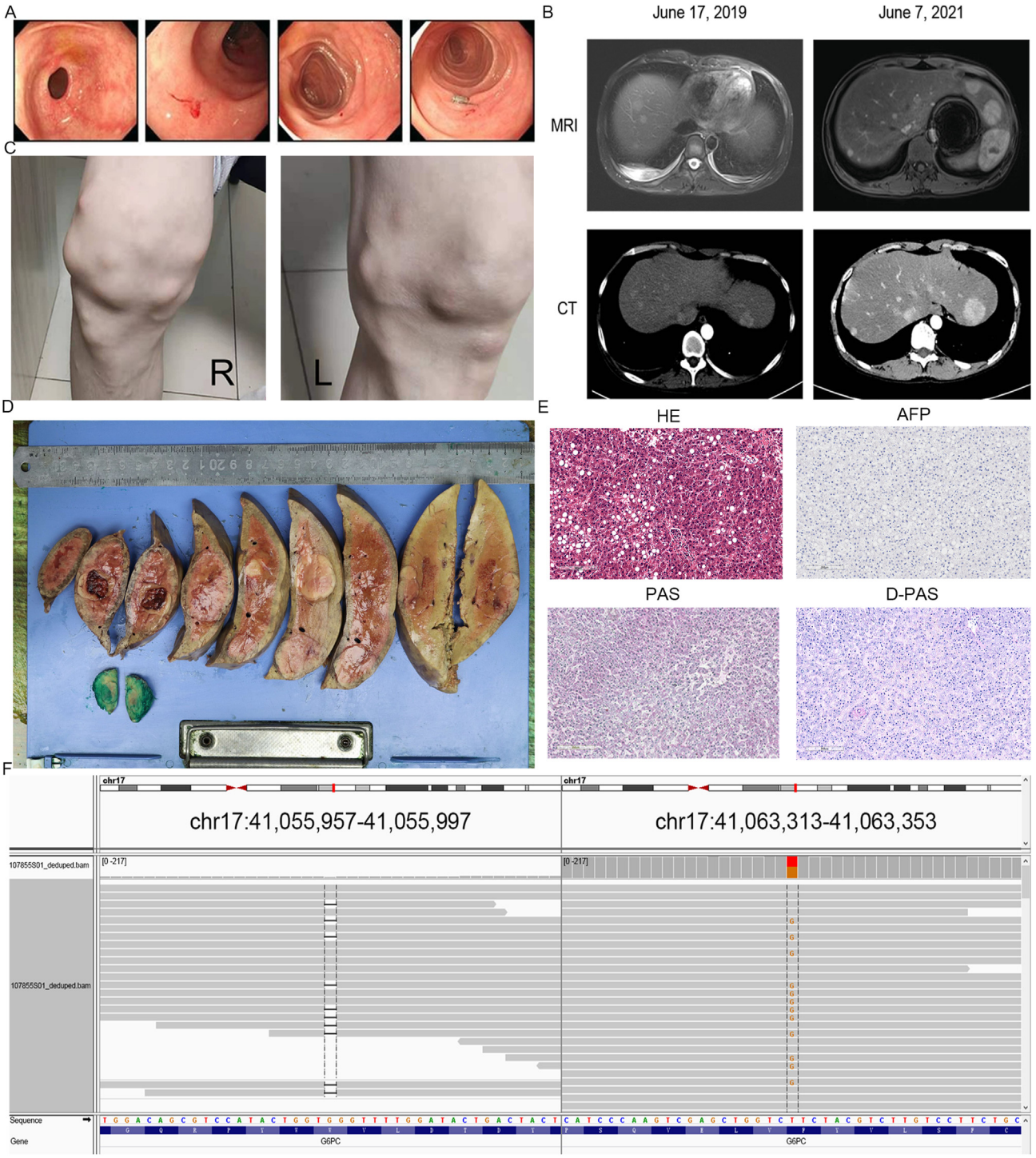

Figure 1 The whole process of diagnosis and treatment of patients and the corresponding results. **(A)** Hemostasis under gastroscope. **(B)** From June 17, 2019, to June 7, 2021, after two years of follow-up, the number and volume of hepatic adenomas increased. **(C)** Preoperative examination showed multiple gout nodules and multiple xanthomas on the back and large joints. **(D)** Multiple hepatic adenomas can be seen in the section of postoperative specimens. **(E)** Immunohistochemical staining showed AFP (−). Special staining showed PAS (+), and D-PAS (−). **(F)** The results of Whole Exome Sequencing (WES) showed that the patient carried the c.262del frameshift mutation of the G6PC1 gene and showed gene variation at the following two chromosome positions: chr17: 41055977, NM_000151: Exon2 c.262del: p.V88Ffs * 14 and chr17: 41063333, NM_000151: Exon5 c.964T > G: p.F322V.

immunohistochemical staining showed Arginase (+), Hepatocytes (+), CD34 (+), AFP (−), CK7 (−), MUC1 (+), β-Catenin (+) and GS (−), respectively. Special staining showed reticular fiber staining (no significant widening of the liver plate), PAS (+) and D-PAS (−), which was consistent with GSDs (Fig. 1E; Fig. S1). The results of Whole Exome Sequencing (WES) showed that the patient carried the c.262del frameshift mutation of the G6PC1 gene and had gene variation in the following two chromosomal positions: chr17: 41055977, NM_000151: Exon2 c.262del: p.V88Ffs * 14 and chr17: 41063333, NM_000151: Exon5 c.964T > G: p.F322V (Fig. 1F).[2] Combining clinical features and genetic background evidences, the patient was diagnosed as GSD-IA. The patient recovered well after the operation and was discharged after diet adjustment and health education.

Main complications of GSD-IA are fasting hypoglycemia, hyperuricemia, hyperlactatemia and hyperlipidemia (especially hypertriglyceridemia).[3] These symptoms are deceptive, especially in some adult patients. Studies suggested that disorders of glycogen degradation may affect primarily the liver and the muscle. The patient's blood Glu level at admission was 3.57 mmol/L, which was consistent with the typical fasting hypoglycemia of GSD-IA. The patient showed hepatic lipid metabolism disorders. TC 6.65 mmol/L, TG 8.93 mmol/L and NEFA 1.1391 mmol/L were higher than normal levels, which are common complications of GSD-IA. In conclusion, the patient exhibited most of the known GSD-IA complications. Combining with the patient's 5-year history of gout, multiple gout nodules and multiple xanthomas on the back and large joints, we speculated that the patient's gout may be related to hyperuricemia caused by metabolism disorder. But drug therapy relying only on NSAIDs is difficult to fundamentally treat treat arthralgia caused by gout, and there will be a risk of recurrence of upper gastrointestinal bleeding.

Up to date, metabolic disturbances in GSD-IA patients can be adequately controlled with diet and adjunctive drug therapy.[4] Uncooked cornstarch is a widely used treatment method for GSD-IA, which releases carbohydrate slowly to prolong the length of euglycemia between meals. In a retrospective study of 231 patients with GSD-IA and 57 patients with GSD-IB, dietary therapy was able to maintain normal glycemia at night, and few patients died from acute metabolic disorders. The studies showed that the underlying pathological process remains uncorrected despite controlling hypoglycemia. Renal disease and liver adenomas are two major causes of morbidity and mortality in patients with GSD-I. Although complications are still common, dietary therapy is the basic therapy. We also followed this principle in the dietary management of the patient.

Diagnosing GSD-IA based on clinical signs and laboratory examinations alone are not enough. At present, the final diagnosis of GSD-IA mainly depends on Whole Exome Sequencing.[5] This technique not only captures the mutated genetic locus, but also determines its type. In this case, we identified gene mutation locations of G6PC1 through whole exome sequencing (WES). The results showed that the G6PC1 gene showed gene variation at the following two chromosome positions: chr17: 41055977, NM_000151: Exon2 c.262del: p.V88Ffs * 14 and chr17: 41063333, NM_000151: Exon5 c.964T > G: p.F322V. Combining genetic test results and clinical signs, the patient was diagnosed as GSD-IA.

In this study, we described one patient of GSD-IA, including clinical course and molecular tests. Based on the results of our molecular investigation, the patients got precise diagnosis and efficient medical management. Like all genetic diseases, GSDs is incurable. Although gene therapy is in the exploratory stage, it's expected to be one possible cure for GSD. We reporting GSD-IA is aiming to get more awareness and knowledge about rare diseases and help to establish standard therapeutic approaches, thus improving prognosis of this rare genetic disease.

Ethics declaration

This case report was approved in full by the Ethics Committee of the Zhongnan Hospital of Wuhan University (Wuhan, China). Written informed consent was obtained from this patient. Data were collected from the daily medical nursing records by staff experienced in gathering clinical information.

Conflict of interests

The authors have declared that no competing interests exist.

Funding

This work was supported by the National Natural Science Foundation of China (NSFC, No. 81702407/H1617), Fundamental Research Funds for the Central Universities of Ministry of Education of China (No. 2042017kf0054) and the Hubei Chenguang Talented Youth Development Foundation (HBCG), China.

Acknowledgements

We thank Yufeng Yuan who provided part of the patient's clinical data in this case report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gendis.2022.08.002.

References

1. Ai J, He W, Huang X, et al. A case report of acute pancreatitis with glycogen storage disease type IA in an adult patient and review of the literature. *Medicine (Baltim)*. 2020;99(42):e22644.
2. Xu S, Qin S, Gu X, et al. Rapid detection of glycogen storage disease type Ia by DNA microarray. *Clin Chem Lab Med*. 2010;48(9):1229−1234.
3. Szymańska E, Jóźwiak-Dzięcielewska DA, Gronek J, et al. Hepatic glycogen storage diseases: pathogenesis, clinical

symptoms and therapeutic management. *Arch Med Sci*. 2021; 17(2):304—313.
4. Derks TGJ, Rodriguez-Buritica DF, Ahmad A, et al. Glycogen storage disease type Ia: current management options, burden and unmet needs. *Nutrients*. 2021;13(11):3828.
5. Kishnani PS, Sun B, Koeberl DD. Gene therapy for glycogen storage diseases. *Hum Mol Genet*. 2019;28(R1):R31—R41.

Maohui Yin[a,1], Lei Chang[a,**], Ping Jiang[a], Zhiyong Yang[a], Zhonglin Zhang[a], Wanyu Zhang[b,1], Zhisu Liu[a,*]

[a] *Department of Hepatobiliary and Pancreatic Surgery, Zhongnan Hospital of Wuhan University, Wuhan, Hubei 430062, China*

[b] *Department of Pathology, Zhongnan Hospital of Wuhan University, Wuhan, Hubei 430071, China*

*Corresponding author.

**Corresponding author.
E-mail addresses: reniorchang@whu.edu.cn (L. Chang), liuzs53@sina.com (Z. Liu)

10 January 2022
Available online 22 August 2022

[1] These two authors made the same contribution.