AACE Clinical Case Rep. 11 (2025) 113–116

Clinical Case Reports™
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Case Report

Improvement of Glycogenic Hepatopathy With Minimal Corresponding Improvement of Glycemic Control in a Person With Type 1 Diabetes: Case Report and Literature Review

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ARTICLE INFO

Article history:
Received 7 October 2024
Received in revised form
25 November 2024
Accepted 12 December 2024
Available online 17 December 2024

Key words:
type 1 diabetes mellitus
liver diseases
glycogen

ABSTRACT

Background/Objective: Glycogenic hepatopathy is characterized by diffuse glycogen accumulation in hepatocytes that leads to hepatomegaly and elevated transaminases. Notably, the condition is reversible as improving glycemic control has been shown to resolve glycogenic hepatopathy and provide symptomatic relief.
Case Report: A 30-year-old female with longstanding and poorly-controlled type 1 diabetes presented to her primary care physician for a routine follow-up visit. Routine lab work demonstrated hyperglycemia and elevated liver enzymes (alkaline phosphatase of 180 U/L, aspartate aminotransferase of 111 U/L, and alanine aminotransferase of 101 U/L). At laboratory reassessment 3 weeks later, liver function tests remained elevated and hepatic ultrasound was unrevealing. She was referred to gastroenterology for further evaluation and laboratory tests for viral and autoimmune hepatitis were negative while magnetic resonance imaging of the abdomen was unremarkable. Given the nondiagnostic work-up, liver biopsy was performed and pathology was consistent with glycogenic hepatopathy. She was referred to Endocrinology for improved glycemic control; however, liver enzymes normalized over the next several months despite minimal improvement in glycemic control. She was eventually transitioned to a closed-loop automated insulin delivery system and started dulaglutide for management of obesity. Subsequent A1c values significantly improved and liver enzymes remained within normal limits.
Discussion: This case raises awareness of an under recognized complication of type 1 diabetes and challenges conventional thinking about factors leading to its resolution.
Conclusion: Further investigation into the underlying pathophysiology of glycogenic hepatopathy is needed.

Introduction

Glycogenic hepatopathy (GH) was first identified in 1930 as the hallmark pathologic finding of Mauriac Syndrome,[1] a condition initially seen in pediatric patients with poorly-controlled type 1 diabetes (T1D) that was characterized by delayed growth, cushingoid features, hypercholesterolemia, hepatomegaly, and elevated liver transaminases.[1,2] GH itself is a benign and potentially reversible condition caused by diffuse deposition of glycogen within hepatocytes that subsequently leads to hepatomegaly, right upper quadrant pain, and elevated liver transaminases.[3,4]

The pathophysiology of GH is poorly understood but is generally believed to be secondary to recurrent fluctuations in glucose and insulin levels. Along these lines, two combined events (*ie*, hyperglycemia and resultant hyperinsulinemia) are present in people with T1D and poor glycemic control that promote hepatic glycogen

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GH, glycogenic hepatopathy; HbA1c, Hemoglobin A1c; T1D, type 1 diabetes.

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https://doi.org/10.1016/j.aace.2024.12.004

deposition and predispose to the development of GH.[5] In hyperglycemia, glucose passively enters the hepatocytes by insulin-independent glucose transporter 2 and is rapidly phosphorylated, resulting in inhibition of its release from hepatocytes.[5,6] Then, increased insulin administration promotes the polymerization of glucose-6-phosphate by glycogen synthase, leading to a large amount of glycogen synthesis in the presence of high cytoplasmic glucose concentrations.[5,7] Glycogen is therefore trapped within the hepatocytes, and the consequent liver damage results in the release of aminotransferases into the plasma.[5]

Strict glycemic control is the cornerstone of GH therapy, and most cases demonstrate complete clinical and biochemical resolution within 2-14 weeks of glycemic improvement.[8-11] Here, we present a case of biopsy-confirmed GH in a patient with T1D that showed resolution more than a year prior to significant improvement in glycemic control.

Highlights

- Glycogenic hepatopathy is an under recognized complication of type 1 diabetes
- Most cases demonstrate complete resolution within weeks of glycemic improvement
- We report resolution of glycogenic hepatopathy with mild reduction of glycemia

Clinical Relevance

Glycogenic hepatopathy is an underappreciated complication of type 1 diabetes that generally resolves with improved glycemic control. We report an atypical resolution of glycogenic hepatopathy that did not correspond to significant improvement in glycemic control. This case highlights the need for further investigation into the underlying pathophysiology of this condition.

Case Report

A 30-year-old female with longstanding and poorly-controlled T1D (s/p multiple episodes of diabetic ketoacidosis and microvascular complications of neuropathy and microalbuminuria), celiac disease (well-controlled on gluten-free diet), and prior history of obesity (treated with Roux-en-Y gastric bypass surgery) presented to her primary care physician for a routine follow-up visit. Initial T1D diagnosis occurred at age 15 years and was confirmed by a c-peptide value that was <0.1 ng/mL. Initial management strategy included multiple daily injections (*ie*, prandial and basal insulin injections). Over the years, the patient reported personal matters that hindered glycemic control (including poor dietary habits and fear of hypoglycemia that led to intentional under-dosing of insulin) and was reflected by persistently elevated Hemoglobin A1c (HbA1c) values (Table). Routine lab work ordered at this follow-up visit demonstrated an elevated blood glucose of 612 mg/dL, alkaline phosphatase (ALP) of 180 U/L, aspartate aminotransferase (AST) of 111 U/L, and alanine aminotransferase (ALT) of 101 U/L. Anthropometric data revealed that her body mass index (BMI) was in the overweight category (Table). The patient reported that she had not consumed any alcohol for at least 3 years prior to these labs being drawn and had not taken any hepatotoxic medications. The primary care physician informed her of the elevated glucose value and instructed her to increase insulin doses and check fingerstick glucose values hourly over the next 4-5 h to ensure glucose returned to appropriate levels. The primary care physician also recommended a contingency plan of returning to the Emergency Department for further evaluation and management if glucose values did not improve.

At laboratory reassessment 3 weeks later, liver function tests remained elevated with an ALP of 201 U/L, AST of 109 U/L, and ALT of 123 U/L (Table). BMI had slightly increased and was now in the obese category (Table). Hepatic ultrasound demonstrated a heterogeneous, coarse background echogenicity possibly related to underlying diffused hepatocellular dysfunction. She was then referred to gastroenterology for further evaluation, given the persistent elevated liver enzymes and nondiagnostic ultrasound result.

At initial evaluation with gastroenterology, she reported mild nausea and new-onset right upper quadrant abdominal pain. A repeat liver ultrasound demonstrated no significant changes compared to prior results. Laboratory tests for viral hepatitis, autoimmune hepatitis (antimitochondrial antibody, antinuclear antibody, anti-smooth muscle antibody), Wilson's disease and alpha-1-antitrypsin deficiency were all negative. Magnetic resonance imaging and magnetic resonance cholangiopancreatography of the abdomen then showed normal morphology of the liver without hepatomegaly or biliary pathology. Given the non-diagnostic work-up, liver biopsy was performed and pathology

Table
Anthropomorphic and Biochemical Data Throughout Treatment

Date	BMI (kg/m^2)	HbA1c (%)	AST (U/L)	ALT (U/L)	ALP (U/L)
12-14-2020	29.87	10.9	111	101	180
01-07-2021	30.14	–	109	123	201
02-17-2021	–	–	164	244	383
05-19-2021	28.32	10.1	–	–	–
03-09-2022	34.60	10.4	44	40	106
07-27-2022	33.34	11.4	–	–	–
01-31-2023	31.52	–	27	52	111
02-16-2023	–	11.3	–	–	–
After Initiation of Closed-Loop Automated Insulin Delivery					
05-03-2023	34.35	8.4	–	–	–
07-26-2023	37.31	–	22	34	118
10-26-2023	36.74	8.7	45	41	97
01-29-2024	33.11	–	19	25	87
05-06-2024	33.51	7.5	–	–	–
10-02-2024	30.62	7.9	33	23	78

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; HbA1c = Hemoglobin A1c.

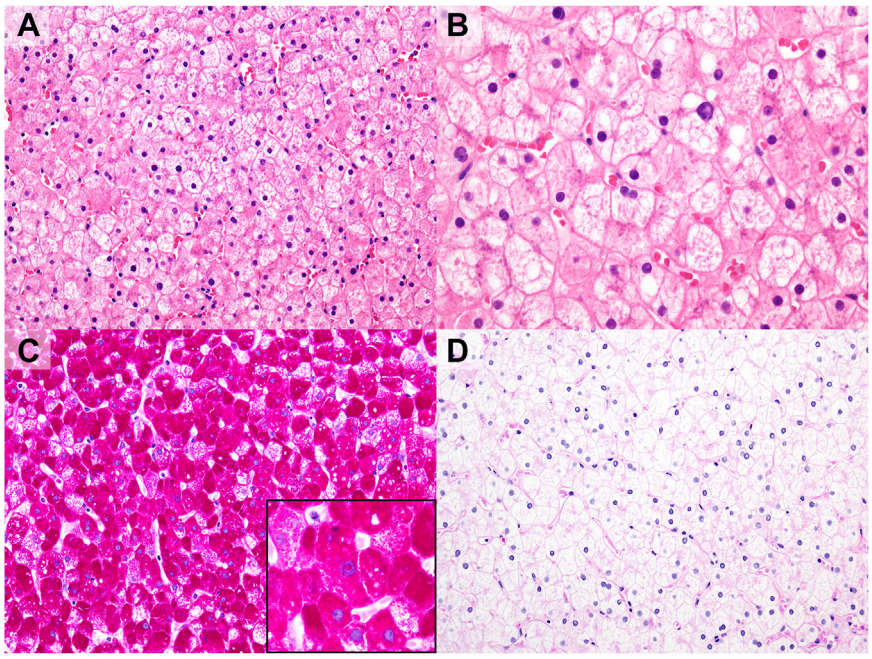

Fig. Hematoxylin & eosin-stained sections revealed hepatocyte enlargement, diffuse clearing of the hepatocyte cytoplasm, and prominent cytoplasmic membranes (*A*: 200×; *B*: 400×). Periodic acid-Schiff (PAS) staining highlights abundant intracellular glycogen (*C*: 200×), including glycogenated nuclei (*C*, inset: 400×). The presence of glycogen is confirmed by absence of staining on PAS with diastase (*D*: 200×).

revealed diffuse clearing of the hepatocyte cytoplasm by abundant intracellular glycogen with minimal macrovesicular steatosis and no fibrosis (Fig.). GH was subsequently diagnosed and she was referred to our Endocrinology Clinic for assistance with diabetes management.

She established care with us shortly after liver biopsy and initiated continuous glucose monitoring to guide titration of insulin doses. She remained on multiple daily injections and despite continuous glucose monitoring use and self-reported adherence to her diabetes treatment plan, glycemic control only minimally improved, and BMI increased (Table). Interestingly, her liver enzymes began downtrending and eventually normalized despite HbA1C values remaining > 10% (Table). The improvement in liver enzymes was accompanied by resolution of her clinical symptoms. She was eventually transitioned to a closed-loop automated insulin delivery system and started dulaglutide for management of obesity. Subsequent A1c values significantly improved and liver enzymes remained within normal limits (Table).

Discussion

Herein, we described a patient with uncontrolled T1D and GH that spontaneously resolved with only minimal improvement (and subsequent worsening) of corresponding glycemic control. We could only find 3 prior reports that described resolution of GH in the setting of minimally-improved glycemic control.[8,12,13] In the first, Chandel *et al* described a case quite similar to ours where a 12-year-old female with poorly-controlled T1D developed GH that clinically resolved over 3 months while HbA1c only decreased from 10.5% to 10.3%.[12] In the second, Parmar *et al* detailed a 21-year-old female with T1D and GH that saw symptomatic relief of abdominal pain and a decline in liver enzymes after a decrease of just 0.6% in HbA1c.[13] In the third, Cha *et al* reported a case series of 3 people with T1D and GH that improved without HbA1c falling < 11%.[8] While HbA1c values did not fall below 11% in these 3 cases, it should be noted that the observed improvements in liver enzymes did correspond to improved HbA1c values overall in 2 of 3 cases reported.[8] Of note, the case report by Parmar *et al* mirrored ours in that both patients had concomitant celiac disease. To our knowledge, no studies have evaluated a potential link between GH and celiac disease in people with T1D. This could be an area for further study, given that individuals with other liver diseases (*eg*, metabolic dysfunction-associated steatotic liver disease (MASLD) and autoimmune hepatitis) also have higher rates of celiac disease.[14,15] Here it should be noted that the association between celiac disease and GH in this population could simply be “true, true, and unrelated” and reflect the fact that people with T1D have higher rates of each diagnosis. For example, people with T1D have higher rates of celiac disease given that the 2 conditions share a common genetic background found in the human leukocyte antigen genotype.[16]

The current report, along with other cited cases of GH resolving with only minimal improvement in glycemic control,[8,12,13] challenge the conventional thinking around GH and raise the question of whether heretofore undefined pathophysiologic factors beyond glycemic control alone may contribute to its resolution. Sherigar *et al* have elegantly pointed out that GH is believed to be a consequence of recurrent fluctuations in glycemia defined by both hyper- and hypoglycemia along with intermittent hyperinsulinemia,[17] a milieu often seen in patients with T1D and poor glycemic control. Moreover, it is well-established that a relative balance between available glucose and insulin is needed for proper function of the glycogen pathway.[18] While our case report cannot prove this theory, we hypothesize that the early stages of improving glycemic control (defined by restoring a more physiologic balance between insulin and glucose) are likely key in stimulating glycogenolysis and resolving GH. If true, this hypothesis holds important clinical ramifications given that the proper approach to therapy for such patients may involve a more physiologic approach to improving glycemic control (*ie*, increasing time-in-range by reducing both hypo- and hyperglycemic excursions) as opposed to administering large doses of insulin in attempt to improve glycemia as quickly as possible.

The prevalence of GH is unknown and almost certainly underappreciated because of its clinical and biochemical overlap with MASLD.[13] For example, both GH and MASLD frequently present with hepatomegaly and elevation of aminotransferase levels without overt impairment of hepatic function.[13] Differentiation of GH from MASLD is imperative, given the differing prognoses and treatment strategies for each condition. Liver biopsy and staining of glycogen using hematoxylin and eosin remains the gold standard for distinguishing between these diagnoses given that key pathologic features of MASLD (*eg*, fibrosis, steatosis, and portal inflammation) are absent in GH.[13] Notably, recent advances in minimally-invasive imaging modalities have led to the recognition that noncontrast computed tomography[19,20] and gradient-dual-echo magnetic resonance imaging of the liver[19] can adequately distinguish GH from MASLD.

Conclusion

This case report described an atypical resolution of GH that did not correspond to significantly improved glycemic control in a patient with T1D. Importantly, this case highlights the need for further investigation into the underlying pathophysiology of GH. Clinicians should be aware of this under recognized condition when they encounter patients with poorly-controlled T1D and unexplained liver enzyme elevations (especially in the lack of typical risk factors for MASLD).

Disclosure

The authors have no conflicts of interest to disclose.

Acknowledgment

We thank the patient for allowing us to share their story with the medical community in hopes to further improve awareness of this underrecognized complication of type 1 diabetes.

Author Contributions

J.T.T. and N.A.R. are co-first authors.

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