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Case Report

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Acute Benign Hepatitis Due to Glycogen Hepatopathy

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ABSTRACT

Glycogen hepatopathy is a very rare and forgotten complication of poorly controlled type 1 diabetes mellitus. Glycogen hepatopathy may also present in type II diabetes mellitus, especially when managed with high doses of insulin. Although it is a benign condition, it is rarely diagnosed in a timely manner. It is characterised by hepatomegaly causing abdominal pain due to stretch on the liver capsule causing capsulitis, and derangement of liver enzymes. In this article we report a patient who presented with severe abdominal pain, hepatomegaly and transaminitis, the symptoms persisted for one year before the diagnosis of glycogen hepatopathy was made.

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Case Report

44-year-old male truck driver presents to ED with right upper quadrant pain in the context of uncontrolled type II diabetes mellitus for the last two years. He denies any weight loss, change in appetite or any changes in bowel motions. He has a past medication history of obstructive sleep apnoea and was unable to comply with CPAP due to night shift. His regular medications include SR Metformin 2g daily, Empagliflozin 25 mg daily, Insulin Lantus variable dose ranged between 50 and 70 units and Atorvastatin 20mg. He has smoked 20 cigarettes a day for the last 20 years and drinks a bottle of wine when he is not working.

On examination in the ED he is haemodynamic stable, febrile and has no signs of chronic liver disease. Chest examination is consistent with chronic obstructive air way disease, and he is noted to have an ejection systolic murmur over the aorta, that radiates to the carotid with a normal second aortic sound. Abdominal examination reveals tender hepatomegaly with a liver span of 25 cm and a smooth and regular surface. No bruit or rubs are noted. Examination of the legs are consistent with length dependant sensory neuropathy. Examination of the fundus shows early diabetic retinopathy in the form of microaneurysm, but no cotton wool exudate or new vascularization. The macula are normal in both eyes.

The patients' blood test reveals a normal full blood count, CRP, ESR, kidney function and normal pH and bicarbonate. Random blood sugar was 17 mmol and HBA1C was 10. Liver panel showed ALT 800 U/L, AST 900 U/L, Bilirubin 17 umol/L, Gamma-GT 290 U/L (<125), INR 1, Albumin 44 g/L (35-40), Total Protein 2.4 g/dL.

Despite a normal bilirubin the patient was given a diagnosis of acute hepatitis. Hepatitis A, B, C, D, E serology, alpha-1 antitrypsin, anti-smooth muscle antibodies, anti LKM, ANA, soluble liver antigen, mitochondrial antibodies, serum ceruloplasmin, 24 hours urinary copper, serum lipase and amylase were ordered, however did not yield any abnormal results. Although iron studies found that ferritin was 1000 and transferrin saturation was 20%.

Given the high AST/ALT ratio, the patient was diagnosed was steatohepatitis and hemochromatosis. The genetic panel for hemochromatosis including C282Yand H63D were negative. A surgical consultation was sought to rule out cholecystitis, which was achieved with ultrasound showing no biliary dilation, no gall bladder wall thickness or pericholecystic. Haematology consultation stated that it was unlikely to be a haematological problem given the normal blood test. Liver service was consulted, who advised for liver biopsy, however this was declined by the patient. The patient was provided supportive care, their dose of insulin was increased and they were booked in for outpatient clinic.

The patients' diabetic control improved to a HbA1c of 8, however their right upper quadrant pain persisted and his AST and ALT continued to become more deranged. Given chronicity of the symptoms, abnormal liver panel and the unavailability of a liver biopsy, the patient was admitted to hospital and treated as seronegative autoimmune hepatitis. The patient was initiated on prednisolone 50 mg daily and an increase of Lantus to BD dose. The abdominal pain got worse and the transaminase doubled. Prednisolone was ceased and the patient started on insulin infusion to control his blood sugar. Paracetamol and slow-release morphine improvement the abdominal pain. Repeated ultrasound showed uniform echogenicity which is common in non-alcoholic fatty liver disease (NAFLD), while computed tomography showed global hyper density which did not support the diagnosis of NAFLD, but rather support the diagnosis of hemochromatosis.

Hepatology and haematology were involved and it was decided that a liver biopsy was required to confirm the diagnosis. A family meeting was arranged with the patients' family and GP in attendance. The patient agreed to a liver biopsy which showed extensive swelling and pallor of hepatocytes, with accentuated cell membranes and massive glycogenation of the nuclei and cytoplasm

with no evidence of fibrosis or parenchymal abnormality. Periodic acid Schiff stain for glycogen was strongly positive, which dissolved with diastase confirming glycogen deposition in the liver. Pearls staining ruled out iron deposition. An MRI confirmed glycogen storage disease in the liver and ruled out other causes of hepatopathy. Patient was treated with metformin, setaglibtin and education about healthy life style with exercise and diet. The abdominal pain abated, liver enzymes improved and blood sugar improved with HBA1c of 7.

Discussion

Glycogen hepatopathy is a very rare and underdiagnosed disease that is usually seen in young person with uncontrolled Type I diabetes mellitus and occasionally in patients with type II DM [1]. Glycogen hepatopathy is not uncommon in type 1 diabetes mellitus with diabetic ketoacidosis, and it has been reported in adults with type II diabetes mellitus with no ketoacidosis [2].

It is a benign and reversible disease, that was first described by Pierre Mauriac in 1930, when a young patient with poorly controlled type 1 diabetes mellitus presented with abdominal pain due to hepatomegaly and capsulitis, poor growth, cushingoid faces and derangement of liver function.

In 2006 Torbenson and colleagues named the disease "glycogenic hepatopathy", which had been universally accepted [3]. Glycogenic hepatopathy generally presents with abdominal pain, deranged liver functions and uncontrolled blood sugar. Patients are usually admitted and subjected to various investigation before reaching the correct diagnosis, and some patients may be discharged without diagnosis. As the disease occurs in young brittle diabetes, not uncommonly, patients will be diagnosed as seronegative autoimmune hepatitis or overlap syndrome.

Glycogen hepatopathy is caused by wide fluctuations of blood glucose and treatment with large doses of insulin [2]. High levels of insulin due to uncontrolled diabetes mellitus or high doses for treatment leads to excess glucose movement into hepatocytes via independent passive diffusion. Increased glucose with the cytoplasm of the hepatocytes are converted to glycogen [3]. Glycogen accumulation in the hepatocytes lead to hepatomegaly and stretch the liver capsule causing right upper quadrant pain and leaking of liver enzymes [4].

Glycogen hepatopathy and NAFLD are clinically indistinguishable. Gradient Dual-Echo MRI can be used to separate these two entities. T1 weighted liver MRI has a characteristic feature and can support the diagnosis in situation where liver biopsy is contraindicated. Despite the recent advances in pathology and imaging, glycogen hepatopathy is only diagnosed by liver biopsy [5, 6]. It is worth mentioning that synthetic liver functions are not affected in glycogen hepatopathy which could narrow the differential diagnosis [7]. A recent small case series found that elevated levels of lactic acid appeared to be a part of the disease process [8]. As hyperlactatemia has recently been regarded as a manifestation of the disease, mitochondrial disease also needs to be considered in the differential diagnosis. Common manifestations of mitochondrial disease are epilepsy, stroke like episodes, mitochondrial encephalopathy, migraine, deafness, cardiomyopathy, maternal inheritance [9,10]. A clue to rule out mitochondrial disease is that glycogen hepatopathy is a curable and reversible diseases [10]. Glycogen hepatopathy had been described in Dumping syndrome, Anorexia nervosa, short term use of high doses of steroid. The main treatment of glycogen hepatopathy is to rule out serious causes of acute hepatitis and to optimise blood sugar control [11].

Conclusion

Glycogen hepatopathy is a very rare diseases and underdiagnosed even by specialists. It is associated with uncontrolled diabetes mellitus. It commonly presents with abdominal pain and high transaminases. Although patients are usually admitted and subjected to various blood tests and imaging, there are often delays in diagnosis with many patients requiring readmission before diagnosis made.

Clinicians should consider glycogen hepatopathy in patients presented with abdominal pain, high transaminases and uncontrolled diabetes mellitus after exclusion of common causes, in addition to normal synthetic liver function, Gradient-Dual-Echo magnetic resonance imaging combined with computed tomography, and improving liver functions after controlling hyperglycaemia. However, liver biopsy remains the only test which can confirm the diagnosis of glycogen hepatopathy].

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