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Case report

Gitelman syndrome: A first published clinical association with chronic pancreatitis, a case report and review of literature

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ABSTRACT

Introduction and importance: Gitelman syndrome (GS) is an autosomal recessive, salt-losing tubulopathy, also referred to as familial hypokalemia-hypomagnesemia, caused by mutation of genes encoding the sodium chloride cotransporter (NCCT) and magnesium transporters in the thiazide sensitive segments of the distal convoluted tubule (DCT) of the nephron. Patients may present with a spectrum of clinical presentations and associations.
Case presentation: Here, we report a case of a 39-year-old female with Gitelman syndrome and chronic pancreatitis in the absence of well-known causes of CP. Her clinical and radiographic profile constituted an indication for surgical intervention, namely pancreatic head and body coring and pancreaticojejunostomy (Frey's procedure) (FP). On follow up 3 month later, the patient is pain-free and is satisfied. To the best of our knowledge and based on literature review, this is the first reported case of GS with CP.
Conclusion: The purpose of this paper is to describe a case of CP in association with established GS as a first published clinical association, raising a possibility of another possible clinical manifestation of GS. Further observational studies are encouraged to support this association.

1. Introduction

Gitelman syndrome (GS) is a rare autosomal recessive, salt-losing tubulopathy, also referred to as familial hypokalemia-hypomagnesemia, characterized by renal potassium wasting, hypokalemia, metabolic alkalosis, hypocalciuria, hypomagnesemia, and hyperreninemic hyperaldosteronism [1–]. Its prevalence is estimated to be 1:40,000 [2,3] caused by mutation of genes encoding the sodium chloride cotransporter(NCCT) and magnesium transporters in the thiazide-sensitive segments of the distal convoluted tubule (DCT) of the nephron [1–3]. English literature review reveals that clinical manifestations of GS are highly variable [1–4,6]. This work has been reported in line with the SCARE 2020 criteria [9].

2. Case report

A 39 years old female known case of Gitelman syndrome was referred to our clinic due to recurrent attacks of acute pancreatitis. She experienced more than 6 attacks in the last 2 years prior to her referral which required hospitalization and non-interventional conservative treatment strategy. The patient had a history of cardiac arrest due to long QT syndrome (LQTS) and chronic hypomagnesemia with successful resuscitation, heart failure, diabetes mellitus, hypothyroidism, latent tuberculosis, and pulmonary embolism 16 years ago. History was negative for alcoholism, gall-stones, and her family history was negative of chronic pancreatitis, medication history of oral magnesium supplement, l-thyroxin and insulin.

2.1. Physical examination

On presentation, the patient was alert and oriented, with a temperature of 37 °C, a pulse of 75/min, and blood pressure of 133/67 mm Hg, O_2 sat. 98% on room air, the rest of the examination was within normal. Laboratory findings were normal, MRCP and abdominal CT showed

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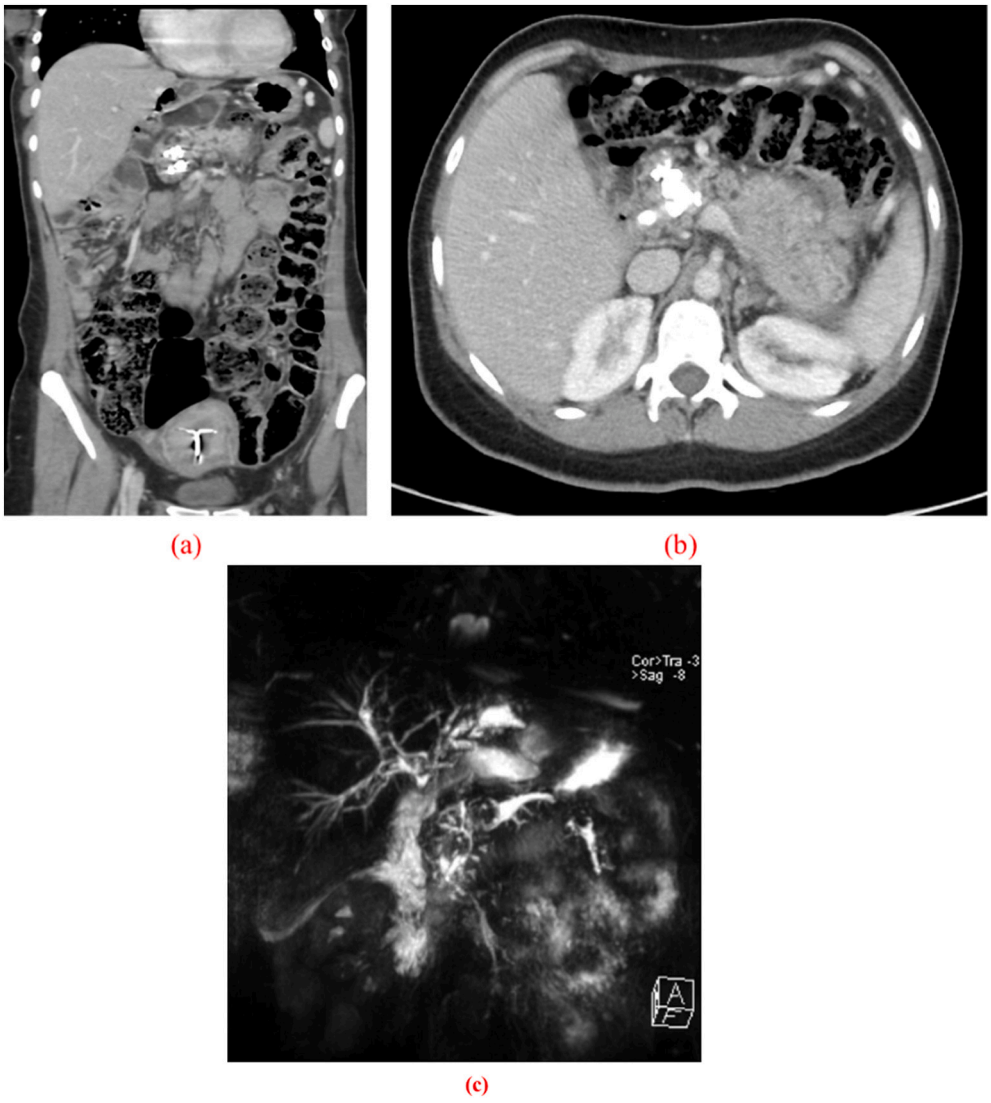

Fig. 1. CT showing diffuse atrophy of pancreas with dilated duct and multiple stones in coronal (a) and axial view (b) MRCP (c).

diffuse atrophy of the pancreas with diffusely dilated main pancreatic duct and branch ducts with multiple pancreatic stones (Fig. 1a, b, c). The maximum diameter of the ductal dilatation reaches up to 0.9 cm. multiple intraductal stones the largest measured 1.2 cm and located within the uncinate process. Additionally, two small intraductal stones were noted at the level of the tail measure 0.1.2 cm. Most of the stones are located at the level of head and uncinate process of the pancreas.

2.2. Treatment course

After discussing the treatment plan, surgery was decided to be the best approach. She underwent exploratory laparotomy, coring out of pancreatic head and body, removal of main pancreatic duct (MPD) all stones, and pancreaticojejunostomy (Frey's procedure). Intra-operative findings were consistent with stony hard pancreas with multiple MPD stones. Postoperatively, she had an uneventful recovery and was discharged home after 3 days on oral magnesium supplement. Pathology report confirmed chronic pancreatitis, fibrosis and acinar cell depletion. On follow-up visits for 3 month, the patient was found to be pain free, completely healthy with a well-healed wound.

3. Discussion

Gitelman syndrome (GS) is a rare autosomal recessively inherited disease and salt-losing tubulopathy, also refers as familial hypokalemia-hypomagnesemia, characterized by hypokalemia, hypomagnesemia, hypocalcemia, hyperreninemia, and hyperaldosteronism, It is caused by mutations of genes encoding the sodium, chloride, and magnesium carriers in the apical membrane of the distal convoluted tubule. The mutations involve 1 - *SLC12A3* gene which encodes the thiazide-sensitive sodium chloride cotransporter (NCCT) 2 - *TRPM6* (Transient Receptor Potential Cation Channel Subfamily M Member 6) gene handles the distal tubular magnesium [1–5]. The impaired reabsorption of sodium and chloride at the thiazide-sensitive sodium chloride co-transporter (TSC) effectively leads to some degree of hypovolemia which in turn activates the renin-angiotensin system, ultimately increasing levels of aldosterone to maintain intravascular volume results in hypokalemia and metabolic alkalosis, as potassium and hydrogen ions are excreted in exchange for sodium, despite the up-regulation of the renin-angiotensin system, patients with GS have normal or low blood pressure [3,5]. TRPM6 channels have an important role in epithelial magnesium transport and in the active magnesium absorption in the gut and kidney the reduction in it expression results in hypomagnesemia seen in GS [1]. Shahzad et al. in their review of 122 cases, 20% of

patients had normal serum magnesium levels [6]. Literature reveals that clinical manifestations of GS are highly variable, most patient presents with nonspecific symptoms of fatigue, generalized malaise, muscle cramps, and cardiac arrhythmias [1,3,4]. Shahzad et al. in 2019 reported GS presented with seizure as the main complain [6], out of 122 patients 5.7% presented with GI-related issues such as anorexia, vomiting, constipation, abdominal pain, and weight loss as the main complaint [6]. Chan et al. in 2020 reported an unusual case of a patient with Gitelman syndrome carrying a germline monoallelic MUTYH c.934-2A>G variant, who subsequently developed multiple neoplasia including colorectal polyposis, synchronous colorectal cancers, recurrent breast fibroadenomas, and a desmoid tumor [2]. GS was also found to be associated with pseudogout and CPPD crystal deposition in about 10% of patients. Other associations included Sjogren's syndrome in 4%, chondrocalcinosis in 3%, and diabetes mellitus (both type 1 and type 2), and primary hyperaldosteronism in about 2% each, and empty sella syndrome in 2 patients [6]. Our reported patient was diagnosed with GS and presented with multiple attacks of acute on top of chronic pancreatitis, despite the negative history of predisposing factors of CP, which is characterized by fibrosis and inflammation of the pancreas in individuals with genetic, environmental, and other risk factors such as smoking, alcohol consumption and hypertriglyceridemia [7,8]. Our case presented with chronic pancreatitis despite the negative history of obvious predisposing factors for CP where she was managed as per current guidelines for chronic pancreatitis. Her background of GS didn't seem to pose a higher morbidity compared to other patients with CP.

4. Conclusions

Gitelman syndrome (GS) is a rare disease that may present with a spectrum of clinical manifestations and associations. Our case highlights the first reported patient of GS concurrently presenting with chronic pancreatitis. Further studies are encouraged to support and/or challenge this association and to better understand the pathophysiology of chronic pancreatitis in patients with Gitelman syndrome.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Ethical approval

This clinical case has been approved by the Institutional Ethics Committee.

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Guarantor

Nourah Mohammed ALSaleh is guarantor of submission and accepts full responsibility.

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CRediT authorship contribution statement

All authors contributed equally to this work including writing and critical revisions.

Declaration of competing interest

None of the authors have any conflict of interest to declare.

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