Journal of Investigative Medicine High Impact Case Reports
Volume 10: 1–3

DOI: 10.1177/23247096221121393
journals.sagepub.com/home/hic
SAGE

Zieve Syndrome: A Clinical Triad, or Perchance a Quartet?

Jonathan Vincent M. Reyes, MD[1], Saad Ahmad, DO[1], Hafsa Majeed, MD[1], Eugenio Kandoth, MD[1], and Joseph J. Lieber, MD[1]

Abstract

Zieve syndrome presents with a triad of hemolytic anemia, unexplained jaundice, and hyperlipidemia secondary to alcohol use/alcohol-induced liver injury, highlighting hemolytic anemia as the hallmark feature. Zieve syndrome is more common than originally perceived as its incidence is estimated to be 1 in 1600 admissions, but its mechanism is still poorly understood. This is a case of a 29-year-old man who developed Zieve syndrome shortly after admission for pancreatitis secondary to alcohol use disorder. Early diagnosis is important to reduce unnecessary tests and interventions. Further studies should be considered to evaluate the association between Zieve syndrome and pancreatitis.

Keywords

diagnostic testing, hospital medicine, gastroenterology, other

Introduction

Since its first description in 1957 by Dr. Leslie Zieve, there have been over 200 published case reports with most cases being misdiagnosed at first presentation, reflecting that this is an under-reported and underdiagnosed syndrome.[1-3] The syndrome appears to be more common than previously thought with an estimated incidence of around 1 in 1600 admissions in general wards based on extrapolation of data from a large tertiary care center in Germany.[4]

Case

A 29-year-old male with no active medical problems other than heavy alcohol use presented with acute epigastric abdominal pain radiating to his back associated with nausea and vomiting. The patient's social history was significant for heavy alcohol use but negative for smoking and illicit drug use. His vital signs on admission were heart rate of 110 bpm, blood pressure 134/78 mmHg, respiratory rate 24, oxygen saturation of 98% on room air, and temperature of 98.5F. A physical exam uncovered jaundice, scleral icterus, and epigastric tenderness. Laboratory findings were significant for an elevated lipase to 2145 U/L (reference range 13-60 U/L), elevated transaminase enzymes aspartate aminotransferase (AST) 163 U/L (reference (5-40 U/L), alanine aminotransferase (ALT) 209 U/L (reference 0-41 U/L), total bilirubin 1.1 mg/dL (reference 0.0-1.2 mg/dL) and direct bilirubin 0.3 (0.0-0.3 mg/dL), HIV negative, ethanol level <10, IgG4 28.3 (within normal limits), triglycerides 62 mg/dL (<150 mg/dL), HbG 15.8 gm/dL (13.5-17.5 gm/dL), Hct 47.8% (41.0%-53.0%), and red cell distribution width (RDW) 15.6% (11.5-14.5%). Abdominal ultrasound was negative for gallstones. Contrast-enhanced computed tomography (CT) of the abdomen/pelvis in the axial plane demonstrates diffuse peripancreatic fat stranding, consistent with acute pancreatitis. Additionally, limited views of the chest demonstrate bilateral small pleural effusions. His acute pancreatitis was managed with in vitro fertilization (IVF) and pain control. Notably, his Bedside Index of Severity in Acute Pancreatitis (BISAP) Score was 1.

On the day after admission, his Hgb dropped from 15.8 to 11.3, without evidence of overt gasrointestinal (GI) bleed; however, an unconjugated bilirubinemia was then appreciated. Labs are noted in Table 1. Total bilirubin increased from 1.1 to 3.2 mg/dL (reference 0.0-1.2 mg/dL) direct bilirubin 1.4 (0.0-0.3 mg/dL) and indirect bilirubin increased from 0.8 to 2.2 mg/dL. Hemolysis labs were significant for lactate dehydrogenase

[1]Department of Internal Medicine, Icahn School of Medicine at Mount Sinai Hospital, Elmhurst Hospital Center, New York, NY, USA

Received January 23, 2022. Revised July 25, 2022. Accepted August 7, 2022.

Corresponding Author:
Jonathan Vincent M. Reyes, MD, Department of Internal Medicine, Icahn School of Medicine at Mount Sinai Hospital, Elmhurst Hospital Center, 79-01 Broadway, New York, NY 11373, USA.
Email: reyesj30@nychhc.org

Table 1. Liver Function Test During Hospital Admission.

Component	Latest reference range and units	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Albumin	3.5-5.2 g/dL	4.9	3.8	3.7	3.3 (L)	3.1 (L)	3.1 (L)	3.2 (L)
Total protein	6.6-8.7 g/dL	7.3	6.2 (L)	5.8 (L)	5.6 (L)	5.3 (L)	5.4 (L)	5.6 (L)
Total bilirubin	0.0-1.2 mg/dL	1.1	1.4 (H)	2.8 (H)	3.2 (H)	3.1 (H)	2.4 (H)	2.1 (H)
Direct bilirubin	0.0-0.3 mg/dL	0.3	0.3	0.9 (H)	1.0 (H)	1.4 (H)	1.0 (H)	1.0 (H)
ALK PHOS	40-129 U/L	129	100	77	72	84	109	156 (H)
ALT (SGPT)	0-41 U/L	209 (H)	130 (H)	81 (H)	54 (H)	43 (H)	45 (H)	65 (H)
AST (SGOT)	5-40 U/L	163 (H)	88 (H)	56 (H)	49 (H)	37	39	56 (H)

Abbreviations: ALK PHOS, Alkaline phosphatase; ALT, Alanine transaminase; SGPT, Serum glutamate pyruvate transaminase; AST, Aspartate aminotransferase; SGOT, Serum glutamic-oxaloacetic transaminase.

(LDH) 1386 (135-225 U/L), haptoglobin <20 (34-200 mg/dL), corrected reticulocyte count 3% (0.5%-2.1%), direct antiglobulin test (DAT) negative, ceruloplasmin level 29 (15-30 mg/dL) within normal limits, fibrinogen elevated to 563 (200-393 mg/dL), and a direct coombs negative. A peripheral smear revealed immature granulocytes, no schistocytes, and occasional nucleated red blood cells (RBCs). The patient continued to receive supportive care and was counseled regarding alcohol cessation. He was discharged with outpatient primary care follow-up.

Discussion

Zieve syndrome presents as an alcohol-related triad of cholestatic jaundice, transient hemolytic anemia, and hyperlipidemia. Patients usually present with anemia in the setting of alcohol use and liver disease. Most cases are associated with right upper quadrant pain and transaminitis or acute pancreatitis.[1,4,5] Some authors report pancreatitis as an essential feature of this syndrome.[3] Other non-specific symptoms include right upper quadrant abdominal pain, nausea, vomiting, malaise, weakness, and low-grade fever. Hyperlipidemia is usually transient and usually subsides within 1 to 2 weeks after initial insult,[1] although atypical presentations are seen in patients where lipids are within normal limits.[2]

Although different theories have been proposed to explain hyperlipidemia and hemolysis in this syndrome, the exact pathogenesis is obscure. Biochemical studies show changes in membrane composition, notably Vitamin E deficiency with a decrease in polyunsaturated fatty acids (PUFAs) results in oxidation of glutathione in RBCs which in turn results in instability of pyruvate kinase enzyme. Additionally, acetaldehyde, a metabolite of alcohol, binds, and inhibits RBC enzymes.[5] The resultant RBC is more susceptible to metabolic injury to circulating hemolysins.[6,7] Previous studies demonstrate hemolysis of autologous and transfused RBCs suggestive role of extracorpuscular hemolytic factors. Furthermore, high levels of circulating lipids, lysolecithin, and lysocephalin act as circulating hemolysins resulting in additional insult to susceptible RBCs.[8] It has been postulated that deficiency of lipoprotein lipase due to damaged pancreatic alpha cells and massive mobilization of lipids in the liver leads to transient hyperlipidemia[3] and subsequent hemolysis and pancreatitis. Hyperbilirubinemia is usually cholestatic secondary to impaired liver metabolism due to alcohol intake.

Diagnosis is usually established by a history of alcohol abuse, clinical triad, and pertinent biochemical tests. Elevation of direct bilirubin, alkaline phosphatase and gamma-glutamyl transferase more than aspartate aminotransferase/alanine aminotransferase can be clues to this diagnosis. Hematology labs reveal anemia, with elevated reticulocytes with an increase in lactate dehydrogenase. Coombs's test is typically negative in Zieve Syndrome. Extensive workup of hemolytic anemia including genetic and biochemical studies is negative. Bone marrow biopsy if performed should demonstrate active marrow proliferation. Follow-up after resolution of the acute phase and complete abstinence demonstrating improvement in hematocrit and hyperlipidemia supports the diagnosis of Zieve syndrome.

Treatment involves supportive care and complete abstinence from alcohol use. Most documented cases recover completely within 4 to 6 weeks of alcohol abstinence.[1,2] It is postulated that alcohol cessation leads to lipid mobilization from plasma to the liver and adipose tissue as lipases are reactivated leading to a slow decrease in plasma triglycerides and metabolic changes in the RBC membrane reducing susceptibility for hemolysis.[9] Plasmapheresis should be considered in patients at high risk of intracerebral hemorrhage and a history of pancreatitis as these patients may be susceptible to acute cerebrovascular events from downstream effects of hyperlipidemia.[9,10]

Conclusion

In Zieve's original report, pancreatitis was frequently suspected but rarely established as CT scans did not yet exist at the time and amylase had poor specificity and sensitivity for acute pancreatitis. Timely recognition of this syndrome may help prevent unnecessary diagnostic or therapeutic interventions. Many cases of Zeives are documented in non-English literature and that's why this syndrome is under-recognized and untreated, therefore there is a real need to increase reporting and awareness that will aid in treating the disease

appropriately. Zieve syndrome and its association with pancreatitis should be suspected in patients with hemolytic anemia in the setting of acute alcohol intake without signs of gastrointestinal bleeding. Future studies should be considered to evaluate the association between Zieve syndrome and pancreatitis.

Authors' Note

This case report was presented virtually as an abstract: *"Zieve syndrome: A Clinical Triad, or Perchance a Quartet?"* at the American College of Gastroenterology national conference in October 2020

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from the patient for their anonymized information to be published in this article.

ORCID iDs

Jonathan Vincent M. Reyes https://orcid.org/0000-0002-2572-6436

Hafsa Majeed https://orcid.org/0000-0001-6565-4038

References

1. Zieve L. Jaundice, hyperlipemia and hemolytic anemia: a heretofore unrecognized syndrome associated with alcoholic fatty liver and cirrhosis. *Ann Intern Med*. 1958;48(3):471-496. doi:10.7326/0003-4819-48-3-471.
2. Abughanimeh O, Kaur A, Numan L, et al. Zieve's syndrome: an under-reported cause of anemia in alcoholics. *Cureus*. 2019;11(2):e4121. doi:10.7759/cureus.4121.
3. Liu MX, Wen XY, Leung YK, et al. Hemolytic anemia in alcoholic liver disease: Zieve syndrome: a case report and literature review. *Medicine (Baltimore)*. 2017;96(47):e8742. doi:10.1097/MD.0000000000008742.
4. Piccini J, Haldar S, Jefferson B. Cases from the Osler medical service at Johns Hopkins University. *Am J Med*. 2003;115(9):729-731.
5. Solomon LR. Effects of acetaldehyde on human red cell metabolism: evidence for the formation of enzyme inhibitors. *Clin Chim Acta*. 1988;175(3):249-265. doi:10.1016/0009-8981(88)90101-5.
6. Goebel KM, Goebel FD, Schubotz R, Schneider J. Red cell metabolic and membrane features in haemolytic anaemia of alcoholic liver disease (Zieve's syndrome). *Br J Haematol*. 1977;35(4):573-585. doi:10.1111/j.1365-2141.1977.tb00622.x.
7. Melrose WD, Bell PA, Jupe DM, Baikie MJ. Alcohol-associated haemolysis in Zieve's syndrome: a clinical and laboratory study of five cases. *Clin Lab Haematol*. 1990;12(2):159-167.
8. Kunz F, Stummvoll W. The significance of plasma phospholipids in Zieve syndrome. *Blut*. 1970;21(4):210-226. doi:10.1007/BF01632304.
9. Choudhry F, Kathawa J, Kerton K, Farshadsefat S, Piper M. Zieve's syndrome presenting with severe hypertriglyceridemia. *ACG Case Rep J*. 2019;6(7):e00133. doi:10.14309/crj.0000000000000133.
10. Hilz MJ, Huk W, Druschky KF, Erbguth F. Fat deposition surrounding intracerebral hemorrhage in a patient suffering from Zieve syndrome. *Neuroradiology*. 1989;31(1):102-103. doi:10.1007/BF00342043.