76144_Auto_EditedC.docx

WORD COUNT	1738	TIME SUBMITTED	06-JUL-2022 11:14AM
		PAPER ID	88067536

Name of Journal: *World Journal of Hepatology*
Manuscript NO: 76144
Manuscript Type: CASE REPORT

Hemorrhagic colitis induced by trientine in a 51-year-old patient with Wilson disease waiting for liver transplantation: A case report

Schult AB *et al*. Hemorrhagic colitis induced by trientine

Andreas Bernd Schult, Matts Andersson, Jorge Asin-Cayuela, Sigvard Olsson

Abstract

BACKGROUND

Wilson disease is a rare inherited disorder of copper metabolism. Treatment consists of chelating agents, but side effects are common. We describe a patient who developed colitis during trientine treatment leading to decompensation of liver cirrhosis.

CASE SUMMARY

A healthy 51-year-old woman was diagnosed with liver cirrhosis due to decompensation with ascites. Etiologic evaluation raised suspicion of hereditary hemochromatosis because of compound heterozygosity *HFE* p.C282Y/p.H63D and phlebotomy was started. Re-evaluation showed low ceruloplasmin, increased urinary copper excretion and the presence of Kayser-Fleischer rings. Wilson disease was confirmed by genetic analysis. Because of decompensated cirrhosis, she was referred for liver transplant evaluation. Simultaneously treatment with trientine was initiated. Liver function initially stabilized, and the patient was not accepted for a liver transplant. Shortly after this, she developed severe hemorrhagic colitis, most probably a side effect of trientine. During that episode, she decompensated with hepatic encephalopathy.

Because of a second decompensating event, she was accepted for liver transplantation, and an uneventful transplantation was carried out after clinical improvement of colitis.

CONCLUSION

Despite Wilson disease being a rare disorder, it is important to consider because it can present with a plethora of symptoms from childhood to high age. Colitis should be recognized as a serious adverse drug reaction to trientine treatment which can result in decompensated liver disease.

Key Words: Wilson disease; Colitis; Trientine; Liver transplantation; Adverse effect; Case report

Schult AB, Andersson M, Asin-Cayuela J, Olsson S. Hemorrhagic colitis induced by trientine in a 51-year-old patient with Wilson disease waiting for liver transplantation: A case report. *World J Hepatol* 2022; In press

Core Tip: Even if Wilson disease is a rare disorder it is important to consider as a cause of liver disease. Treatment with chelating agents is associated with multiple side effects and colitis should be recognized as a serious adverse drug reaction to trientine. Such serious adverse event can trigger hepatic decompensation with the need for liver transplantation.

INTRODUCTION

Wilson disease (WD) is a rare recessively inherited disorder in which toxic amounts of copper accumulate in the liver and the brain due to a defective excretion to the bile[1]. It is caused by mutations in the *ATP7B* gene, impairing copper excretion into bile. The prevalence of WD is estimated to be between 1 case in 10000 to 30000 live births[2]. WD can manifest with neuropsychiatric symptoms, chronic liver disease or acute liver failure. Treatment usually consists of copper chelating agents, such as penicillamine and trientine, or zinc, which reduces enteric copper uptake. Patients with decompensated liver cirrhosis or acute liver failure may require liver transplantation which corrects the underlying metabolic defect[3].

CASE PRESENTATION

Chief complaints

The present case was a 51-year-old married woman with two children who was employed as a worker at a warehouse. She had never smoked and consumed 1-2 glasses of wine per week. On a routine health check at age 50, the local general practitioner rewarded her star for excellent health. However, shortly afterward, she began to feel fatigued and swollen and was diagnosed with ascites at her local hospital.

Physical examination

She was not jaundiced.

Laboratory examinations

The liver function tests showed slightly elevated bilirubin (30 μmol/L, reference 5-25) and albumin was decreased to 20 g/L (reference 36-45). Alkaline phosphatase was within the normal range, alanine aminotransferase (ALT) normal and aspartate aminotransferase (AST) just above the upper limit of normal, resulting in an AST/ALT ratio > 2. Because of a prothrombin time/international normalised ratio of 1.9, a liver biopsy was not undertaken.

Viral hepatitis was ruled out by serology, and negative autoantibodies (antinuclear, smooth muscle and antimitochondrial) made autoimmune hepatitis and primary biliary cholangitis unlikely. A negative phosphatidylethanol confirmed the absence of harmful drinking[4]. Transferrin saturation was 52% and ferritin 206 µg/L (reference 13-150), hence hereditary hemochromatosis (HH) was considered. Genetic analysis showed *HFE* p.C282Y/p.H63D compound heterozygosity and iron removal by phlebotomy was initiated. There was a slight improvement, but after three months, her liver tests were still abnormal, which led to the consideration of other diagnoses.

The suspicion of WD was supported by a low serum ceruloplasmin concentration (0.14 g/L, reference 0.22-0.58) and increased urinary copper excretion (4.8 µmol/24 h, reference 0.15-0.60). Detailed eye examination revealed the presence of Kayser-Fleischer rings. Genetic analysis of *ATP7B*, covering all coding exons +/- 25 flanking intronic bases, showed the presence of two heterozygous pathogenic variants, namely c.3207C>A, p.(His1069Gln) and c.2305A>G, p.(Met769Val) (NM_000053.3). The analysis was carried out on DNA extracted from blood after enrichment with a custom-made next-generation sequencing gene panel that included *ATP7B* (SureSelectQXT, Agilent TechnologiesR), on a MiSeq instrument (IlluminaR). Results were verified by Sanger sequencing. Compound heterozygosity of the two variants was confirmed by genotyping of the patient's parents.

FINAL DIAGNOSIS

She was diagnosed with liver cirrhosis due to decompensation with ascites.

TREATMENT

Upon confirmation of WD, the patient underwent neurological evaluation. Besides slight numbness of legs, especially at night, there were no neurologic symptoms. A complete neurological exam showed a slightly decreased blink rate and somewhat abrupt saccades. There were no signs of dysarthria, gait abnormalities or parkinsonism.

Chelating treatment with trientine 300 mg bid was initiated. Simultaneously, the patient was referred for liver transplant evaluation at Sahlgrenska University Hospital, Gothenburg, due to decompensated liver cirrhosis. At the time of evaluation, she had been on treatment with trientine for six weeks. She was free from ascites on low-dose diuretics and had no other decompensating events. Her model for end-stage liver disease score was 13 and Child-Pugh class B (8 points). Because of stable disease during ongoing treatment, she was not accepted for liver transplantation.

However, on the day of leaving the university hospital, loose stools appeared. During the following days, her symptoms worsened, and her stools became bloodstained. At her local hospital, a sigmoidoscopy showed hemorrhagic colitis. Biopsies were negative for cytomegalovirus (CMV), and stool cultures returned negative. As colitis has been described as a side effect of trientine[5,6], the drug was withdrawn and treatment with prednisolone 30 mg q.d. initiated.

Her colitis improved rapidly, but after some days, she became somnolent. There were no clinical signs of gastrointestinal bleeding, spontaneous bacterial peritonitis or other infection. A cranial computed tomography showed normal findings, and electroencephalography was compatible with metabolic encephalopathy. A diagnosis of hepatic encephalopathy West Haven grade 3 was made. The patient improved on treatment with lactulose and rifaximin. Treatment with zinc acetate 25 mg t.i.d. to reduce copper absorption was started. Steroids were tapered within one week. She was again referred for transplant evaluation and subsequently accepted.

OUTCOME AND FOLLOW-UP

After another episode of severe hepatic encephalopathy requiring intubation, liver transplantation with a whole graft from a deceased donor was carried out three months later. Vessel reconstruction consisted of a side-to-side cavo-caval, end-to-end artery and duct-to-duct biliary anastomosis. Immunosuppressive induction therapy was given by 1000 mg methylprednisolone intraoperatively and 20 mg basiliximab before reperfusion and on postoperative day (POD) 4. Mycophenolate mofetil 1 g b.i.d. was started before

transplantation, and tacrolimus was introduced on POD 4. No steroids were used for maintenance immunosuppression. The clinical course was uneventful, and the patient was discharged to home on POD 10.

During the first month, a mild acute T-cell mediated rejection (rejection activity index 3) was treated with oral corticosteroids. Because of CMV mismatch (D+/R-), she received prophylaxis for six months with valganciclovir 450 mg q.d. After discontinuation of prophylaxis, she developed CMV disease with pancytopenia and oral treatment with valganciclovir was reinstated. After viral clearance, the further course was uneventful. Protocol liver biopsy after one year only showed mild inflammation without sign of rejection or fibrosis. Up to now, three years after liver transplantation, there have been no further complications, and the patient is now back to normal active life.

DISCUSSION

This case illustrates two important learning points. The first one is the difficulty to diagnose WD. It can present with both neuropsychiatric as well as acute or chronic liver disease. Because WD is a rare disease, it may not be included in differential diagnosis of liver disease although its prevalence is probably significantly higher than the number of clinically diagnosed cases[7]. A delayed diagnosis is not uncommon, as in another Swedish female observed during family screening of HH[8] in which WD was confirmed by sequencing of ATP7B showing homozygosity for the variant c.3207C>A (His1069Gln)[9].

An initial diagnosis of HH was feasible because this is a common disorder in central Sweden[10] and the patient had elevated ferritin. However, compound heterozygosity HFE p.C282Y/p.H63D seldom results in HH-related morbidity[11]. Comorbid factors should always be considered, and WD has previously been reported in the patient's home area[12].

The other point is the awareness of potential side effects of trientine. Although drugs for the treatment of WD were introduced in the 1960s, there is still a lack of high-quality

studies. Initial treatment of patients not presenting with acute liver failure usually aims at promoting urinary copper excretion with chelating agents. Penicillamin is a drug with high incidence of adverse reactions as hypersensitivity, gastrointestinal symptoms, proteinuria and bone marrow depression with rare cases of aplastic anemia.

Trientine is often used as a first-choice treatment because of less side-effects compared to penicillamine[3]. It is, however, not an uncomplicated drug, and besides skin reactions and neurologic worsening, cases of colitis have been described[5,6]. New compounds for the treatment of WD are under development[13,14] and may widen the available armamentarium, offering alternative therapies in case of adverse drug reactions.

Our patient developed severe hemorrhagic colitis due to trientine treatment, which may have triggered decompensation of her liver cirrhosis. Decompensated liver cirrhosis and acute liver failure are indications for liver transplantation in patients with WD. It can only be speculated on if liver transplantation could have been avoided if the patient had not developed severe colitis. However, after improvement of colitis with steroid treatment, the patient could undergo liver transplantation with excellent functional status after three years of follow-up.

CONCLUSION

Even if Wilson disease is a rare disorder, it is important to consider because it can present with a plethora of symptoms from childhood to high age. Colitis should be recognized as a serious adverse drug reaction on trientine treatment that can result in decompensated liver disease.

76144_Auto_EditedC.docx

ORIGINALITY REPORT

6%
SIMILARITY INDEX

PRIMARY SOURCES

1	Karl Sigvard Olsson, Olof Wålinder, Andreas Kindmark, Roger Williams. "Common local founder effects for Wilson's disease and hereditary hemochromatosis; mutation studies of a large family", Scandinavian Journal of Gastroenterology, 2012 Crossref	42 words — 2%
2	www.lidsen.com Internet	19 words — 1%
3	"Poster Abstracts", American Journal of Transplantation, 2011 Crossref	14 words — 1%
4	G. Porro, J. Hoffmann, D. Wittebol-Post, A.J.F. Schenk Rootlieb, O. van Nieuwenhuizen, W.F. Treffers. "A new and simple method for testing the monocular and binocular visual field in cerebral palsy (CP): our experience on 31 children in a clinical setting", Clinical Neurology and Neurosurgery, 1997 Crossref	10 words — 1%
5	www.wjgnet.com Internet	10 words — 1%
6	ccforum.biomedcentral.com Internet	9 words — < 1%

7 Karin J. Blakemore. "Maternal Genetic Disorders That Affect Fetal Health", Wiley, 2021
Crossref

8 words — < 1%

EXCLUDE QUOTES	OFF	EXCLUDE SOURCES	OFF
EXCLUDE BIBLIOGRAPHY	OFF	EXCLUDE MATCHES	OFF