

Journal of Nephroathology



Bile cast nephroathy; a neglected entity

Rodrigo Alvarez¹, Ramin Tolouian^{2*}

¹Department of Medicine, College of Medicine, University of Arizona, Tucson, USA

²Renal Section, Southern Arizona VA Health Care System and College of Medicine, University of Arizona, Tucson, AZ, USA

ARTICLE INFO

Article type:
Review

Article history:
Received: 13 July 2023
Accepted: 23 August 2023
Published online: 17 September 2023

Keywords:
Bile cast, Nephroathy, Hepatorenal syndrome, Cholemic nephrosis, Jaundice associated nephroathy, Acute kidney injury

ABSTRACT

This study investigates the role of bile cast nephroathy (BCN) in acute kidney injury associated with cholestatic liver disease. Bile cast nephroathy is characterized by kidney injury due to, bile-related factors, distinct from hepatorenal syndrome (HRS) linked to hemodynamic changes in liver disease. The mechanisms of BCN include oxidative damage, tubular toxicity, and obstructive physiology. Diagnosis is typically through biopsy, although alternatives like trans-jugular biopsy are considered due to bleeding risks. Treatment targets underlying causes of hyperbilirubinemia, and extracorporeal therapies like plasmapheresis and molecular adsorbent recycling system show potential efficacy. Awareness and further research on noninvasive diagnostic methods for BCN are recommended.

Implication for health policy/practice/research/medical education:

Bile cast nephroathy (BCN) is characterized by kidney injury due to, bile-related factors, distinct from HRS linked to hemodynamic changes in liver disease. The mechanisms of BCN include oxidative damage, tubular toxicity, and tubular obstruction.

Please cite this paper as: Alvarez R, Tolouian R. Bile cast nephroathy; a neglected entity. J Nephroathol. 2023;12(4):e21522. DOI: 10.34172/jnp.2023.21522.

Introduction

The role of cholestatic liver disease and its association with acute renal insufficiency must be better understood. Bile cast nephroathy (BCN), also known as cholemic nephrosis (CN) was first described by Quincke in 1899 in an autopsy of patients with jaundice and renal insufficiency (1,2). BCN is an acute kidney injury usually because of hepatic dysfunction or liver disease, although indirect hyperbilirubinemia from red blood cell destruction could also play a role. It is well known that hemodynamic changes, in the setting of liver diseases such as hepatorenal syndrome (HRS), play a crucial role in kidney function mainly as a result of splanchnic dilation from increased vasodilators such as nitric oxide. The vasodilators, in turn, lead to decreased systemic vascular resistance resulting in pre-renal azotemia, as is seen in cases of HRS (3). However, often overlooked and independent of HRS, bile salts and bile casts may lead to physiologic obstruction, further exacerbating kidney damage. It is recorded that extensive hyperbilirubinemia, usually total bilirubin greater than

20 mg/dL, may lead to BCN. In situations of end-stage liver disease, it may be an automatic response to associate acute renal failure with HRS. However, although kidney injury is likely a result of multiple processes, it is essential to acknowledge the distinct pathophysiologic process differences between HRS and BCN. HRS is triggered by portal hypertension, which is presumed to produce vasodilators in the splanchnic circulation with resultant activation of renin-angiotensin-aldosterone system leading to intra-renal vasoconstriction and eventually acute kidney injury. On the other hand, bile nephroathy is presumed to be secondary to insults to the kidney, including direct toxicity from bile acids and obstructive physiology (4). Early recognition of this disease may provide earlier treatment and symptom reversal, ultimately leading to a better prognosis.

Discussion

Most of the bile acids reabsorb in the ileum, and via portal circulation, reach the liver. A portion of the reabsorbed bile

*Corresponding author: Ramin Tolouian,
Email: ramin.tolouian@va.gov

acids that are not taken by the liver are then filtered by the kidneys and either reabsorbed or excreted in the urine (2). In the cases of significant hyperbilirubinemia with acute kidney injury, one should consider BCN as a concomitant driving force to the kidney injury. The exact process of bile nephropathy needs to be better understood. However, there are multiple postulated mechanisms. During states of hyperbilirubinemia, hepatocytes and proximal tubules change to excrete excess bile. It is hypothesized that, there is a limit to the amount of bilirubin transported in the proximal tubules before they become saturated. Excess bilirubin then exerts oxidative damage on the tubular cell membranes, which is evidenced by tubular hypertrophy, as reported by 73.5% of autopsies of jaundiced patients.

Furthermore, histology findings have also supported architectural changes, including hypertrophy, swelling, and hyperplasia of the parietal layer of Bowman's capsule. Mitochondrial oxidative phosphorylation can also be affected by bilirubin. It can lead to the uncoupling of oxidative phosphorylation, thus decreasing adenosine triphosphate (ATP) production, further leading to tubular damage and mitochondrial injury with altered penetration. Due to systemic and renal hemodynamics, hyperbilirubinemia has also been associated with kidney injury (2,4). Some studies performed on mice have demonstrated both ionotropic and chronotropic effects as a direct result of systemic hyperbilirubinemia. It is thus feasible that the commonly present HRS in liver disease, in conjunction with the proposed hemodynamic changes associated with bilirubin, could contribute to decreased peripheral vascular resistance and reduced renal blood flow resulting in profound kidney injury (2,5). There is evidence to support that bile acids cause inhibition of Na-H, Na-K, and Na-Cl pumps, which promotes cast formation, which named BCN. In conjunction with Ph changes in the proximal tubules and loops of Henle, BCN further exacerbates tubular toxicity and injury. In an *in vivo* mice study involving common bile duct ligation, renal tubular epithelial injury was noted to occur predominately at the level of aquaporin 2-positive collecting ducts suggesting most of the injury occurring in the distal collecting system (5).

In one clinicopathologic study of 44 subjects with jaundice, van Slambrouck et al observed that 24 of them (55%) had bile casts in renal distal tubules. Bile cast formation was strongly correlated to higher bilirubin levels but not statistically significant with elevated liver enzymes or serum creatinine. In this study, 7 (17%) patients had gross jaundice on examination, and all seven had BCN. This finding suggests that gross jaundice could correlate to a degree with BCN. Additionally, 10 (23%) of patients had cirrhosis secondary to alcoholic hepatitis, and all patients with alcoholic hepatitis had pathology compatible with

BCN suggesting some association of alcoholic hepatitis with BCN. HRS was diagnosed in 13 (30%) of patients, of which 11 (85%) had bile casts, further supporting the prevalence of concomitant kidney insult in such patients from the physiologic process of HRS. Various methods of insulting the tubules, such as oxidative damage, hemodynamic changes, and obstructive physiology, have been proposed. It is thus important to bring awareness to the neglected BCN and the implications of acute kidney injury that are often present in conjunction with other physiologic processes, such as HRS, in the setting of liver failure (6). Although definitive diagnosis may be challenging, earlier recognition and knowledge of BCN may lead to improved outcomes.

Diagnosics treatment/management

The definitive diagnosis of BCN is made through a kidney biopsy. It has been observed that the medulla and cortex of the kidney are yellow in patients with BCN, and then they turn to green after fixation by formalin (7). Most of the pathology is microscopically limited to the tubules with little to no glomerular abnormalities (2,8). Van Slambrouck et al, also observed bile cast deposition in 36% of distal tubules as opposed to 15% in proximal tubules. This difference might be explained by a higher concentration of bilirubin and lower pH in the microenvironment of distal tubules (6).

Although the gold standard for diagnosis is a biopsy, it carries a significant risk, especially in coagulopathic patients, which tends to correlate with underlying liver disease. Thus, it is rarely done in these situations. A trans-jugular renal biopsy might be considered an alternate procedure instead of a traditional percutaneous biopsy. Trans jugular biopsy has been reported to have a diagnostic tissue adequacy of 95.8% with a complication of 1% (9). Additionally, the diagnosis of BCN can be highly suspected when there is evidence of bile crystals on urinalysis. Urinary neutrophil gelatinase-associated lipocalin (NGAL) expression is upregulated in kidney proximal tubule cells following ischemic injury and is suitable for monitoring tubular epithelial damage. Interleukin 18 and kidney injury molecule 1, liver-type fatty acid binding protein, are biomarkers that require more research but could be potentially used for kidney injury tubular markers and aid in a prompt diagnosis of kidney injury in the setting of BCN (2).

There are currently no established treatment guidelines for diagnosing BCN. Treatment primarily revolved around treating the underlying cause of hyperbilirubinemia to prevent kidney injury. In cases of biliary stones, procedures such as endoscopic retrograde cholangiopancreatography, stent placements, or tumor resection may be conducted if appropriate. Alternatively, extracorporeal therapies

are possible treatment options. Therapies such as plasmapheresis and albumin dialysis can reduce inflammatory cytokines and bilirubin levels through filtration. Keklik et al have published their experience with plasma exchange as a treatment option for patients with severe hyperbilirubinemia; however, cessation of plasmapheresis results in a rebound of hyperbilirubinemia (10). A molecular adsorbent recycling system is another method that uses albumin-enriched dialysate to remove the albumin-bound toxins from the blood selectively. Molecular adsorbent recycling system has been used as a potential bridge to liver and kidney transplants (11). Some extracorporeal biologic devices use liver cells from humans and porcine to support the failing liver through detoxification (12). Traditional medical therapies such as Lactulose, cholestyramine, steroid, and ursodeoxycholic acid have only shown minimal improvement (8).

Conclusion/Recommendations

Bile cast nephropathy is not a common diagnosis, probably due to a lack of awareness, misdiagnosis, or mislabeling. In real day to day medical practice, acute kidney injury in a setting of liver failure falls under the HRS. BCN or Jaundice-associated nephropathy is challenging as renal biopsy is the gold standard to diagnose, and these populations tend to bleed. Although trans jugular renal biopsy is considered an alternative, it still has a high chance of complication and bleeding. Future studies should focus on noninvasive modalities, such as potential biomarkers for diagnosing BCN.

The primary pathophysiology of BCN revolves around tubulopathy due to tubular damage from bile salts, obstruction, high bilirubin, and renal hemodynamic changes. BCN should be considered in patients with plasma bilirubin concentrations of >20 mg/dL, specifically in patients who do not respond to HRS treatment. Treatment options are limited, with a focus on the treatment of the underlying cause. Current literature supports extracorporeal therapies such as plasmapheresis or more novel therapies like molecular adsorbent recycling system or plasma filtration adsorption dialysis. Ultimately, the goal is to bring awareness and promote advancement in diagnostics for BCN while recognizing that, in certain instances, treatment will be based on the reversal of liver injury, which may include a transplant.

Authors' contribution

Conceptualization: Rodrigo Alvarez and Ramin Tolouian.

Data curation: Rodrigo Alvarez and Ramin Tolouian.

Investigation: Ramin Tolouian.

Resources: Ramin Tolouian.

Supervision: Ramin Tolouian.

Validation: Ramin Tolouian.

Visualization: Rodrigo Alvarez and Ramin Tolouian.

Writing—original draft: Rodrigo Alvarez.

Writing—review and editing: Ramin Tolouian.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

Funding/Support

None.

References

- Patel J, Walayat S, Kalva N, Palmer-Hill S, Dhillon S. Bile cast nephropathy: A case report and review of the literature. *World J Gastroenterol.* 2016;22:6328-34. doi: 10.3748/wjg.v22.i27.6328.
- Somagutta MR, Jain MS, Pormento MKL, Pendyala SK, Bathula NR, Jarapala N, et al. Bile Cast Nephropathy: A Comprehensive Review. *Cureus.* 2022;14:e23606. doi: 10.7759/cureus.23606.
- Ginès P, Schrier RW. Renal failure in cirrhosis. *N Engl J Med.* 2009;361:1279-90. doi:10.1056/NEJMra0809139.
- El Chediak A, Janom K, Koubar SH. Bile cast nephropathy: when the kidneys turn yellow. *Renal Replacement Therapy.* 2020;6:15. doi:10.1186/s41100-020-00265-0.
- Fickert P, Krones E, Pollheimer MJ, Thueringer A, Moustafa T, Silbert D, et al. Bile acids trigger cholemic nephropathy in common bile-duct-ligated mice. *Hepatology.* 2013;58:2056-69. doi:10.1002/hep.26599.
- van Slambrouck CM, Salem F, Meehan SM, Chang A. Bile cast nephropathy is a common pathologic finding for kidney injury associated with severe liver dysfunction. *Kidney Int.* 2013;84:192-7. doi:10.1038/ki.2013.78.
- Krones E, Pollheimer MJ, Rosenkranz AR, Fickert P. Cholemic nephropathy - Historical notes and novel perspectives. *Biochim Biophys Acta Mol Basis Dis.* 2018;1864:1356-66. doi: 10.1016/j.bbadis.2017.08.028.
- Betjes MG, Bajema I. The pathology of jaundice-related renal insufficiency: cholemic nephrosis revisited. *J Nephrol.* 2006;19:229-33.
- Cluzel P, Martinez F, Bellin MF, Michalik Y, Beaufile H, Jouanneau C, et al. Transjugular versus percutaneous renal biopsy for the diagnosis of parenchymal disease: comparison of sampling effectiveness and complications. *Radiology.* Jun 2000;215:689-93. doi: 10.1148/radiology.215.3.r00ma07689.
- Keklik M, Sivgin S, Kaynar L, Pala C, Solmaz M, Cetin M, et al. Treatment with plasma exchange may serve beneficial effect in patients with severe hyperbilirubinemia: a single center experience. *Transfus Apher Sci.* 2013;48:323-6. doi: 10.1016/j.transci.2013.04.009.
- Sens F, Bacchetta J, Rabeyrin M, Juillard L. Efficacy of

extracorporeal albumin dialysis for acute kidney injury due to cholestatic jaundice nephrotoxicity. *BMJ Case Rep.* 2016;2016:bcr2015213257. doi: 10.1136/bcr-2015-213257.

Extracorporeal liver support with molecular adsorbents recirculating system in patients with severe acute alcoholic hepatitis. *J Hepatol.* 2003;38:24-31. doi: 10.1016/s0168-8278(02)00334-3.

12. Jalan R, Sen S, Steiner C, Kapoor D, Alisa A, Williams R.

Copyright © 2023 The Author(s); Published by Society of Diabetic Nephropathy Prevention. This is an open-access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.