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The pathophysiology of neonatal jaundice in urosepsis is complex with mixed bilirubin!!!

Abstract

Urinary tract infection is one of the most common type of infections in neonates, with the capacity to induce neonatal jaundice which is another major emergency in neonates. However, the pathophysiology of this comorbidity is still poorly described in neonatology and the clinical implications insufficiently illustrated. The aim of this review is to contribute to shed more light over this issue in order to improve understanding and orientate therapeutic interventions. In this piece of work, we did a critical study of recent and pertinent articles on the topic available online. This enabled us to make a synthesis of current classifications of neonatal jaundice, with epidemiological, etiological and pathophysiological aspects of the comorbidity with urosepsis being discussed. We conclude with consequent therapeutic implications.

Keywords: Jaundice, neonatal sepsis, urinary tract infection

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Introduction

Neonatal jaundice has a particular semiological value in pediatrics with major clinical implications. These include neuro-cerebral complications with kernicterus, hepatic lesions with cirrhosis, and renal affection with acute kidney injury mainly from potential cholemic nephropathy.[1-4] Nevertheless, particular complications are more common with specific hyperbilirubinemia, be it conjugated (direct) or unconjugated (indirect). These entail possibilities of urgent intervention with phototherapy and/or exchange-transfusion or not.[1-4] Attempts to classify jaundice type with predominant bilirubin according to common etiologies exist and may be very important for clinical orientation. The association of neonatal jaundice with sepsis and precisely with urinary tract infection (Urosepsis) has been demonstrated in various ways.[2,4] However, either types of hyperbilirubinemia have separately been identified from one study to the other, without a publication synthesizing the clinical relevance of this particular findings. This justifies the present article with updated review.

Background

Neonatal jaundice or icterus may be defined as a yellowish pigmentation of the skin, mucous membranes and sclera, occurring within the first 28 days of life. It could be classified according to its mode of onset and course in time. Its intensity may be subjectively appreciated from physical exam and precise biochemically from serum analysis.[1] In effect, jaundice in neonates may be precocious within the first 24 hours of life, be of early onset within 7 days of life or of late onset as from the 8th day after birth, and is said to be prolonged when it persists for more than 15 days.[2-4] From the clinical stand point, neonatal jaundice may have a cephalo-caudal progression, being mild when limited to the cephalic extremity (the face mainly), moderate when only the face and the trunk are concerned and severe when the whole body is involved. Nevertheless, it might be better defined biochemically as hyperbilirubinemia in neonates with values >12 mg/l. Even though, jaundice may only become clinically evident when total blood bilirubin is around 29-41mg/l (50-70 µmol/l).[1]

Jaundice is a common sign in neonates and is most often physiological and benign, occurring in almost 60% of neonates especially within the first week of life. This with unconjugated bilirubin, principally from polycythemia with shortened erythrocytes' half-life, poor liver conjugation or bilirubin displacement from glucuronidation by fatty acids from breastmilk.[5] Other pathological causes of jaundice with indirect bilirubin include pre-hepatic hemolytic etiologies such as ABO, Rh or rare blood groups incompatibility, constitutional abnormalities of red blood cells (enzymopathies of which G-6 PD and pyruvate kinase deficits, cytoskeleton anomalies as elliptocytosis and spherocytosis), cephalhematoma or blood caput succedaneum resorption and sepsis mainly.[5,6] On the other hand, neonatal jaundice with mixed direct and indirect bilirubin are due to intrahepatic specific alterations of bilirubin conjugation in hepatic cells (Gilbert and Crigler-Najjar syndromes, hepatitis, drugs intoxictaion) or anomalies of bilirubin secretion into biliary canals (Dubin-Johnson and Rotor syndromes, cystic fibrosis, alpha-1 antitrypsin deficiency, Alagille disease, Niemann-Pick disease, galactosemia).[5,6] Moreover, post-hepatic causes of neonatal jaundice may occur as well, including biliary atresia and other malformations, cholangitis as inflammation, cholangiocarcinoma as most frequent neoplasia and gall bladder stones from metabolism just to name a few. Nevertheless, endocrine disorders such as hypothyroidism may equally be responsible for jaundice in neonates.[5,6] Jaundice may be aggravated by any disorder of homeostasis including hypoxia (SPO2 < 85%), hypothermia, hypoglycemia, hemodynamic disorders, acidosis, hypoprotidemia, plasmatic hyperosmolarity, and hypothyroidism.

Among sepses involved with neonatal jaundice, urinary tract infection is described as one of the most frequent, with incidence as high as 21%.[7] This occurs with either forms of bilirubin. Although some researchers' specifically investigated direct bilirubin as being associated with urosepsis, a considerable number of studies included neonatal jaundice without distinction.[8-10] It has been described that indirect bilirubin might be predominant at the beginning of the infection, while direct bilirubin continuously rises in concentration as the infection progresses.[8-10] The most commonly identified bacteria in neonates with urinary tract infection and jaundice are gram negative, among which Escherichia coli and Klebsiella pneumonia are the most frequent.[8] They are followed by Pseudomonas aeruginosa, acinetobacter bacilli as gram negative, and staphylococcus aureus, as well as enterococcus which are rather gram positive bacteria.[8-10]

Escherichia coli is particularly predominant in urosepsis with cholestatic or direct bilirubin perhaps with a more pronounced hepatic tropism. In general, the comorbidity is most frequent in the male sex, as uncircumcision increases the risk of onset by more than 9 folds.[8-10] Urinary tract infection in neonates may be responsible for all forms of jaundice from precocious onset to persistent.[8] Although pyuria may occur with incidence as high as 50%, neonates with urinary tract infection may only have jaundice as unique sign.[10-12] Jaundice in neonates with urosepsis may have a poor response to phototherapy, which may take more time compared with other etiologies.[8] The minimal but systematical laboratory tests to perform in neonates with precocious and early onset jaundice in an emergency context should include total and conjugated blood bilirubin, blood groups for mother and baby, full blood count, indirect Coomb's test, CRP, blood and urine culture.[9-12]

Discussion of pathophysiology

Jaundice in urosepsis seems to result from the direct effect of bacteria, is enhanced by their toxins and maintained by the host response through pro-inflammatory cytokines. All bacteria actually identified in urosepsis causing jaundice are able to secrete hemolysin, a toxic protein which causes erythrocyte destruction and the release of their hemoglobin content into the blood stream.[13] Hemoglobin in blood stream is then successively transformed into biliverdin and indirect bilirubin through the actions of the enzymes heme oxygenase and biliverdin reductase respectively.

On the other hand, bacteria in the blood stream during sepsis migrate to the liver where they can cause direct hepatocellular damage with hematological release of both direct bilirubin from ruptured hepatocytes and indirect bilirubin due to interrupted conjugation.[14] Moreover, lipopolysacharidic (LPS) endotoxins from bacterial capsules are released into the blood stream during bacterial replication or lysis by the host defense.[15] LPS endotoxin have direct impact on hepatocytes and Kupffer cells through nuclear receptors and transcription factors which lead to downregulation of transporters involved in bile flow.[16] The most important transporters that are downregulated in sepsis include canaliculi transporters known as Multidrug Resistance-associated Protein 2 (MRP2) and Bile Salt Export Pump (BSEP), which are all ATP-dependent and involved in the export of bile salts in the liver and biliary system.[15–19] This alteration is responsible for cholestasis with impaired bile excretion susceptible to damage hepatocytes.[20] As a result, important reflux of direct or conjugated bilirubin into the blood stream occur.

The liver seeding with bacteria from urosepsis leads to proinflammatory cytokine release. The resulting hepatic inflammation is responsible for activation of sinusoidal endothelial cells, margination and migration of leukocytes into the liver and the activation of resident macrophages.[21] Overall inflammation with leucocytes products including interleukins (IL-6 and 8 mainly), Tumor Necrosis Factor (TNF-α), Nitric Oxide (NO) from inducible NO synthase occurs. This affects liver functioning, bile metabolism and flow, with cholestasis and release of conjugated bilirubin into the blood stream, causing jaundice.

Furthermore, LPS endotoxins affect the inner circular muscle fibers of the intestines. This hinders peristalsis with a sort of sepsis-induced paralytic ileus and perhaps pseudo occlusion, increasing the entero-hepatic cycle of direct bilirubin, with blood transit and jaundice.[5,19]

Conclusion with therapeutic implications

Based on epidemiological data, it appears that urosepsis is a major cause of all forms of neonatal jaundice and should always be enquired and discussed in such contexts, even in the absence of any other sign. The pathophysiological mechanisms of the comorbidity reveal it is with either forms of bilirubin, and therefore mixed. However, the kinetics of various bilirubin in urosepsis with neonatal jaundice show predominance with indirect bilirubin at the beginning and progressive inversion with direct bilirubin taking over as the infection goes on. From a therapeutic stand point, there is indication for phototherapy according to critical indirect bilirubin levels, especially during the early stages of the infection when the risk of kernicterus is majored. Phototherapy in neonatal jaundice due to urosepssis may be less efficient with regards to duration, when compared with other etiologies. This is because of the complexity of the pathogenesis, including biological interactions with mixed bilirubin, of which rising concentrations of indirect bilirubin is insensitive and can't be regulated by phototherapy. Furthermore, the management of neonatal jaundice in urosepsis must absolutely include antibiotherapy which should be started as early as possible, and targeting gram negative bacteria in priority. These would contribute to prevent acute complications with kernicterus, liver failure and kidney injury.

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Conflict of interest

The authors declare that they have no competing interest.

References

1. Fetus and Newborn Committee, Canadian Paediatric Society. Guidelines for detection, management and prevention of hyperbilirubinemia in term and late preterm newborn infants (35 or more weeks' gestation) summary. *Paediatr Child Health*. 2007;12(5):401–418.
2. Nickavar A, Sotoudeh K. Treatment and prophylaxis in pediatric urinary tract infection. *Int J Prev Med.* 2011;2:4–9.
3. Omar C, Hamza S, Bassem AM, et al. Urinary tract infection and indirect hyperbilirubinemia in newborns. *N Am J Med Sci.* 2011;3:544–547.
4. Mutlu M, Çayır Y, Aslan Y. Urinary tract infections in neonates with jaundice in their first two weeks of life. *World J Pediatr.* 2014; 10:164–167.
5. Erhan Aygün, Emine Yurdakul Ertürk, Özden Aksu Sayman, et al. Evaluation of Etiological, Clinical and Laboratory Findings in Infants with Prolonged Jaundice. *Biomed J Sci & Tech Res.* 2020;31(5).
6. Bilgen H, Ozek E, Unver T, et al. Urinary tract infection and hyperbilirubinemia. *Turk J Pediatr.* 2006;48:51–55.
7. Omar C, Hamza S, Bassem AM, et al. Urinary tract infection and indirect hyperbilirubinemia in newborns. *North Am J Med Sci.* 2011;3:544–547.
8. Özcan M, Sarici SU, Yurdugül Y, et al. Association Between Early Idiopathic Neonatal Jaundice and Urinary Tract Infections. *Clin Med Insights: Pediatr.* 2017;11:1–7.
9. Sarici S, Kul M, Aply F. Neonatal jaundice coinciding with or resulting from UTI? *Pediatrics.* 2003;112(5):1212–1213.
10. Lee HC, Fang SB, Yeung CY, et al. UTI in infants: comparison between those with conjugated vs unconjugated hyperbilirubinemia. *Ann Trop Pediatr.* 2005;25:277–282.
11. Moyo GPK, Sobguemezing D, Adjifack HT. Neonatal Emergencies in Full–term Infants: A Seasonal Description in a Pediatric Referral Hospital of Yaoundé, Cameroon. *Am J Pediatr.* 2020;6(2):87–90.
12. Georges Pius K M, Aurore Albane E, Marie–Paul B, et al. Neonatal Sepsis: Highlights and Controversies. *J Pediatr Neonatal.* 2022;4(1):1–5.

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13. Niazi R, Baharoon B, Neyas A, et al.Unusual Case of an Infant with Urinary Tract Infection Presenting as Cholestatic Jaundice. *Case Rep Nephrol.* 2018;2018:9074245.

14. Eskandari MK, Kalff JC, Billiar TR, et al. Lipopolysaccharide activates the muscularis macrophage network and suppresses circular smooth muscle activity. *Am J Physiol Gastrointest Physiol.* 1997;273(3):727–734.

15. Saeki J, Sekine S, Horie T. LPS–induced dissociation of multidrug resistance–associated protein 2 (Mrp2) and radixin is associated with Mrp2 selective internalization in rats. *Biochem Pharmacol.* 2011;81(1):178–184.

16. Geier A, Fickert P, Trauner M. Mechanisms of disease: mechanisms and clinical implications of cholestasis in sepsis. *Nat clin pract Gastroenterol hepatol.* 2006;3:574–585.

17. Sekine S, Yano K, Saeki J, et al. Oxidative stress is a triggering factor for LPS–induced Mrp2 internalization in the cryopreserved rat and human liver slices. *Biochem Biophys Res Commun.* 2010;399(2):279–285.

18. Hayman J. Jaudice due to bacterial infection. *Gastroenterol.* 1979;77(2):362–374.

19. Eskandari MK, Kalff JC, Billiar TR, et al. LPS–induced muscularis macrophage nitric oxide suppresses rat jejunal circularmuscle activity. *Am J Physiol–Gastrointest Liver Physiol.* 1999;277(2):478–486.

20. Chiou FK, Ong C, Phua KB, et al. Conjugated hyperbilirubinemia presenting in first fourteen days in term neonates. *World J Hepatol.* 2017;9(26):1108–1114.

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