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ABSTRACT

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COGNITIVE IMPAIRMENT CAUSED BY HYPERBILIRUBINEMIA IN ADULT PATIENTS WITH MECHANICAL JAUNDICE SECONDARY TO CHOLEDOCHOLITHIASIS

Background. The neurotoxic effects of bilirubin are well-documented in neonatal jaundice, where hyperbilirubinemia can lead to kernicterus and long-term neurodevelopmental deficits. However, the cognitive impact of hyperbilirubinemia in adults, particularly in the context of mechanical jaundice, remains poorly understood. With the rising prevalence of choledocholithiasis due to lifestyle changes and an aging population, understanding the neurological consequences of this condition is becoming increasingly important.

Objectives. This study aimed to characterize the extent and nature of cognitive dysfunction in adult patients with choledocholithiasis-induced mechanical jaundice and associated hyperbilirubinemia; evaluate the correlation between serum bilirubin concentrations and cognitive performance metrics; and determine the potential reversibility of observed cognitive deficits following therapeutic biliary decompression.

Materials and Methods. Cognitive function was assessed in adult patients with mechanical jaundice secondary to choledocholithiasis using the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). Initial evaluations were conducted after hospitalization, with follow-up assessments performed one week after successful biliary decompression via percutaneous transhepatic cholangiostomy (PTCH) or endoscopic/surgical intervention.

Results. Patients with mechanical jaundice exhibited significantly lower cognitive scores compared to the control group at baseline. A moderate-to-strong positive correlation was identified between total bilirubin levels and the severity of cognitive impairment. Following biliary decompression, cognitive function improved markedly. However, 10.2% of patients experienced persistent mild cognitive deficits despite normalization of bilirubin levels.

Conclusions. Hyperbilirubinemia in adults with mechanical jaundice caused by choledocholithiasis is associated with significant but predominantly reversible cognitive impairment. Early recognition and management, including timely biliary decompression and supportive therapy, are crucial for improving neurological outcomes and enhancing the overall quality of life for affected patients.

Keywords: choledocholithiasis; jaundice, obstructive; cognitive dissonance.

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КОГНІТИВНІ ПОРУШЕННЯ, СПРИЧИНЕНІ ГІПЕРБІЛІРУБІНЕМІЄЮ У ДОРОСЛИХ ПАЦІЄНТІВ З МЕХАНІЧНОЮ ЖОВТЯНИЦЕЮ НА ФОНІ ХОЛЕДОХОЛІТІАЗУ

Актуальність. Нейротоксична дія білірубіну добре досліджена у випадках неонатальної жовтяниці, коли гіпербілірубінемія часто може спричинити ядерну жовтяницю та тривалий дефіцит розвитку нервової системи. Однак у дорослих когнітивні наслідки гіпербілірубінемії залишаються недостатньо вивченими, особливо в контексті механічної жовтяниці. Враховуючи зростання поширеності холедохолітіазу через фактори способу життя та демографічного старіння населення, розуміння неврологічних наслідків цього стану набуває все більшого клінічного значення.

Мета. Оцінити ступінь та характер когнітивних порушень, пов'язаних з гіпербілірубінемією, у дорослих пацієнтів з механічною жовтяницею на фоні холедохолітіазу; дослідити зв'язок між рівнями білірубіну та когнітивними функціями та оцінити оборотність цих порушень після декомпресії жовчних шляхів.

Матеріали та методи. Ми провели дослідження, оцінюючи ступінь та характер когнітивних порушень, пов'язаних з гіпербілірубінемією, у дорослих пацієнтів з механічною жовтяницею на фоні холедохолітіазу. Когнітивні функції оцінювали за короткою шкалою оцінки психічного статусу (Mini-Mental State Examination – MMSE) і монреальською шкалою когнітивної оцінки (Montreal Cognitive Assessment (MoCA). Оцінку проводили після госпіталізації та повторювали через тиждень після успішної декомпресії жовчних шляхів за допомогою черезшкірної черезпечінкової холангіостомії (ЧЧХС) або ендоскопічного/хірургічного втручання.

Результати. На початковому етапі пацієнти з механічною жовтяницею демонстрували значно нижчі когнітивні показники порівняно з контрольною групою. Спостерігалася помірно-сильна позитивна кореляція між рівнем загального білірубіну та тяжкістю когнітивних порушень. Після проведення біліарної декомпресії було відзначено покращення когнітивних функцій. Незважаючи на це, у 10,2% пацієнтів спостерігалось збереження постійного легкого когнітивного дефіциту.

Висновки. Гіпербілірубінемія у дорослих пацієнтів з механічною жовтяницею на фоні холедохолітіазу, пов'язана зі значним, але значною мірою оборотним когнітивним порушенням. Розпізнавання та лікування цих порушень за допомогою ранньої

декомпресії жовчовивідних шляхів і підтримуючої консервативної терапії може покращити не лише неврологічні результати, але й загальну якість життя пацієнтів.

Ключові слова: холедохолітіаз; жовтяниця, механічна; когнітивні порушення.

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INTRODUCTION / ВСТУП

Hyperbilirubinemia, an abnormally high level of serum bilirubin is the main feature of mechanical jaundice, a condition that occurs due to biliary tract obstruction. While choledocholithiasis represents a common etiology of mechanical jaundice, resulting in impaired bile flow and systemic bilirubin accumulation, its potential cognitive implications remain inadequately explored despite well-documented systemic manifestations such as pruritus, fatigue, and coagulopathy. The lipophilic properties of unconjugated bilirubin facilitate its penetration of cellular membranes, including those of neurons and glial cells. Upon cellular entry, bilirubin exerts pernicious effects on mitochondrial function through inhibition of respiratory chain enzymes, particularly cytochrome oxidase, thereby compromising ATP production essential for neuronal function and homeostasis [1–6].

Moreover, bilirubin-induced neurotoxicity extends beyond bioenergetic disruption. The compound significantly impacts neurotransmitter systems through modulation of glutamatergic and GABAergic receptor function, potentially precipitating excitotoxicity and subsequent neuronal injury. Furthermore, bilirubin activation of microglial cells promotes the release of pro-inflammatory cytokines, establishing a persistent inflammatory setting that may exacerbate neuronal damage [5, 6].

While the neurotoxic effects of hyperbilirubinemia have been extensively documented in neonates, particularly in relation to kernicterus and associated neurodevelopmental aftereffects, the cognitive impact of hyperbilirubinemia in adults remains poorly characterized, especially in the context of mechanical jaundice. This knowledge gap warrants particular attention given the increasing prevalence of choledocholithiasis, attributed to contemporary lifestyle factors and demographic aging. Understanding the neurological consequences of this condition has therefore emerged as of increasing clinical importance. [2, 5, 6]

OBJECTIVES

This study aimed to characterize the extent and nature of cognitive dysfunction in adult patients with choledocholithiasis-induced mechanical jaundice and associated hyperbilirubinemia; evaluate the correlation between serum bilirubin concentrations and cognitive performance metrics; and determine the potential reversibility of observed cognitive deficits following therapeutic biliary decompression.

MATERIALS AND METHODS

A prospective observational study was conducted from 2019 to 2023 at the Surgical Department №2 of the Kyiv Municipal Clinical Hospital of Emergency Medical Care. The study population comprised 265 patients (41.82% male, 59.18% female) with a mean age of 55.4 years, diagnosed with mechanical jaundice secondary to choledocholithiasis. Exclusion criteria encompassed pre-existing neurological disorders, hepatic encephalopathy, and concurrent liver diseases (cirrhosis, viral hepatitis).

Cognitive assessment was performed using the Mini-Mental State Examination (MMSE) [7] and Montreal Cognitive Assessment (MoCA) [8, 9]. Evaluations were conducted at admission and one week post-biliary decompression, achieved through percutaneous transhepatic cholangiostomy (PTCH) or endoscopic/surgical intervention. Laboratory parameters, including serum bilirubin levels, liver function tests, and inflammatory markers, were measured at both time points.

A control group (n=50), matched for age and sex, comprised individuals without jaundice to establish baseline cognitive performance.

Statistical analyses were performed using MedStat software. Data are presented as mean ± standard error of the mean (M ± m). Pearson's correlation coefficient was used to analyze the relationship between serum bilirubin levels and cognitive parameters. Changes in cognitive function pre- and post-decompression were assessed using paired t-tests.

The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants after comprehensive explanation of the study's nature, purpose, potential risks, and benefits. Patient confidentiality was maintained throughout the study period.

RESULTS

At baseline, patients with mechanical jaundice exhibited significantly lower cognitive scores compared

to the control group (Table 1). The mean MoCA score in the mechanical jaundice group was 20.3 ± 3.5 versus 26.7 ± 2.1 in the control group ($p < 0.01$). Similarly, MMSE scores were lower in the patient group (24.1 ± 3.8 versus 29.0 ± 1.6, $p < 0.01$).

A moderate-to-strong negative correlation was observed between total serum bilirubin levels and cognitive performance metrics (Table 2). Elevated bilirubin levels correlated with reduced MoCA and MMSE scores ($r = -0.68$, $p < 0.001$).

Table 1 – Baseline Characteristics and Cognitive Scores in Patient and Control Groups (Mean ± SEM)

Parameter	Patient group (n=265)	Control group (n=50)	p
Age	55.4 ± 11.6	53.8 ± 10.7	0.376
Total Bilirubin (μmol/L)	269.2 ± 71.8	11.97 ± 5.13	<0.001
MoCa score	20.3 ± 3.5	26.7 ± 2.1	<0.001
MMSE score	24.1 ± 3.8	29.0 ± 1.6	<0.001

Following biliary decompression, cognitive function showed significant improvement (Table 3). The mean MoCA score increased by 4.2 ± 1.3 points ($p < 0.01$), while the MMSE score improved by 3.9 ± 1.5 points ($p < 0.01$). However, 27 patients (10.2%) demonstrated persistent mild cognitive impairment, defined as MoCA scores below 26, despite normalized bilirubin levels.

Table 2 – Correlation Between Serum Total Bilirubin Levels and Cognitive Performance Metrics

Parameter	Pearson's correlation coefficient (r)	p
Total Bilirubin x MoCA	-0.68	<0.001
Total Bilirubin x MMSE	-0.64	<0.001

DISCUSSION

This study demonstrated significant cognitive impairment in adult patients with mechanical jaundice secondary to choledocholithiasis. Patients exhibited marked deficits in attention, memory and executive function, with significantly lower baseline cognitive scores compared to controls. These impairments, quantified by MoCA and MMSE assessments, showed strong correlation with elevated serum bilirubin levels (Table 2), suggesting bilirubin's potential role as a neurotoxic agent in adults, analogous to its established effects in neonatal jaundice [10, 11].

The significant improvement in cognitive scores following biliary decompression (Table 3) supports the idea of reversibility of bilirubin-induced cognitive dysfunction. Post-decompression increases in MoCA and MMSE scores (mean improvements of 4.2 and 3.9 points, respectively) emphasize the importance of early intervention in preventing neurological sequelae. However, the persistence of mild cognitive impairment in 10.2% of patients despite normalized bilirubin levels suggests potential subclinical neurotoxicity or prolonged recovery periods. This subgroup may represent individuals with increased susceptibility to bilirubin-induced injury or additional contributing factors, such as systemic inflammation or oxidative stress, warranting further investigation.

The correlation between bilirubin levels and cognitive impairment severity (Table 2) aligns with previous studies of hepatic encephalopathy, where neurocognitive dysfunction correlates with metabolic derangements, including hyperammonemia and bilirubin toxicity [12, 13]. However, our findings indicate that hyperbilirubinemia-associated cognitive deficits in mechanical jaundice are predominantly transient and responsive to prompt intervention. The observed variability in cognitive recovery suggests that additional factors, including comorbidities, age, and jaundice duration, may influence outcomes.

Table 3 – Comparison of Cognitive Scores Pre- and Post-Biliary Decompression (Mean ± SEM)

Parameter	Pre-Biliary Decompression	Post-Biliary Decompression	p
MoCA score	20.3 ± 3.5	24.5 ± 2.7	<0.01
MMSE score	24.1 ± 3.8	28.0 ± 2.1	<0.01
Total Bilirubin (μmol/L)	269.2 ± 71.8	84.2 ± 16.1	<0.001

CONCLUSIONS

Hyperbilirubinemia in adult patients with mechanical jaundice secondary to choledocholithiasis is associated with significant yet largely reversible cognitive impairment. However, these impairments may hinder patients' ability to comprehend and adhere to medical recommendations, thereby complicating disease management. Early recognition and prompt treatment through biliary decompression and supportive conservative therapy may not only enhance neurological recovery but also improve overall quality of life [14, 15].

PROSPECTS FOR FUTURE RESEARCH / ПЕРСПЕКТИВИ ПОДАЛЬШИХ ДОСЛІДЖЕНЬ

Further research is warranted to clarify the precise mechanisms underlying bilirubin-induced neurotoxicity and to identify factors contributing to potential residual cognitive deficits. Long-term follow-up studies will be essential in determining whether these impairments fully resolve over time or contribute to persistent cognitive dysfunction.

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

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The authors declare no conflicts of interest related to this study.

ARTIFICIAL INTELLIGENCE DISCLOSURE / ВИКОРИСТАННЯ ШТУЧНОГО ІНТЕЛЕКТУ

No artificial intelligence (AI) technology was used in the writing or editing of this manuscript.

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