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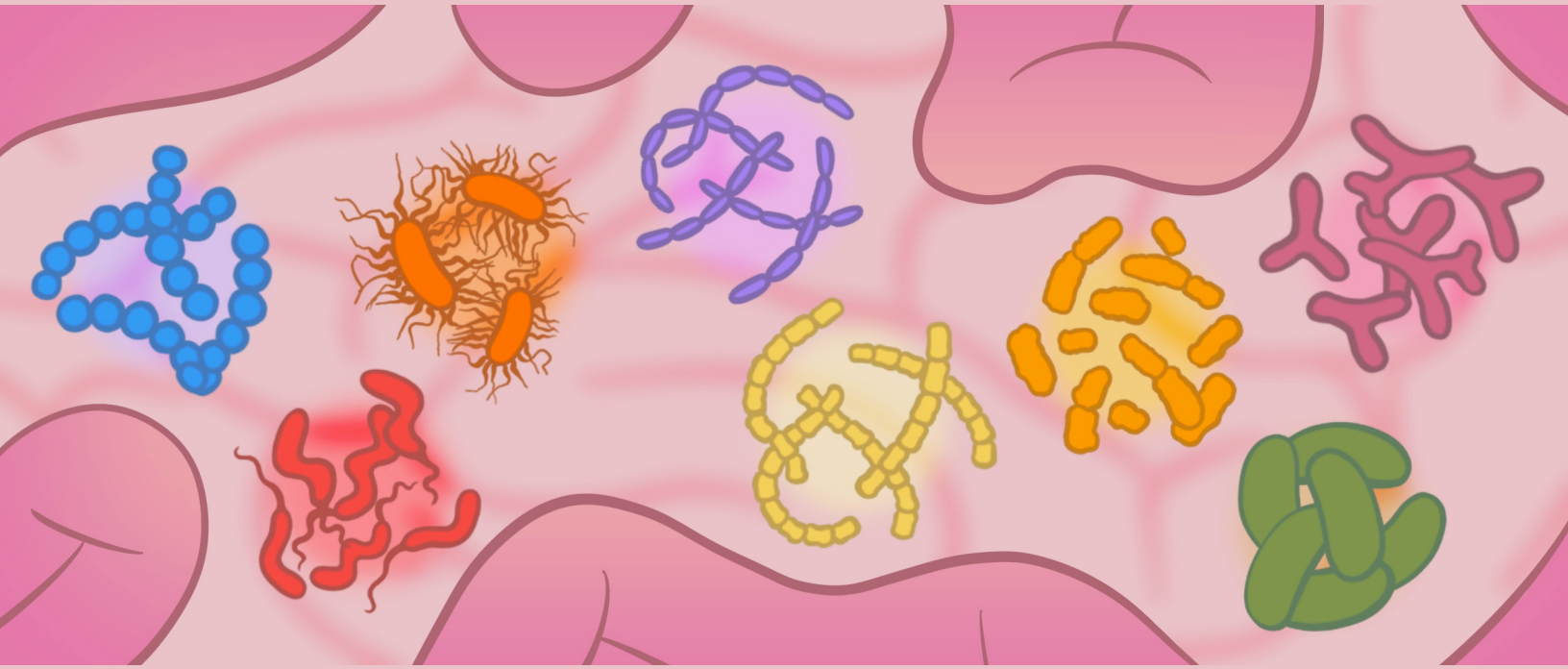

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Original Article

Impact of Biliary Atresia on Neurodevelopment in Children: A Systematic Review

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Abstract:

Background: Survival in children with biliary atresia (BA) has improved substantially, shifting clinical focus toward long-term morbidity, including neurodevelopmental outcomes. However, existing evidence remains fragmented, and prior reviews have not comprehensively addressed motor, behavioral, and autism-related domains. This study aimed to synthesize current evidence on neurodevelopmental outcomes in children with BA across cognitive, motor, and behavioral domains, and to identify clinical factors associated with adverse developmental trajectories.

Methods: A systematic search of PubMed, Scopus, and Wiley was conducted from database inception to October 17, 2025, following PRISMA 2020 guidelines. Observational studies reporting neurodevelopmental outcomes in children (≤18 years) with BA were included. Risk of bias was assessed using the Newcastle–Ottawa Scale and the Joanna Briggs Institute checklist. Due to substantial heterogeneity, a narrative synthesis was performed.

Result: Seven studies involving infants to adolescents with BA were included. Motor impairment was the most consistent finding, detectable from early infancy and persisting into later childhood. Cognitive outcomes were heterogeneous, ranging from significant impairment to age-appropriate or above-normative performance in selected cohorts. Behavioral and adaptive difficulties, including attention problems and autism spectrum–related traits, were frequently reported. Markers of disease severity such as unsuccessful Kasai portoenterostomy (KPE), delayed jaundice clearance, growth failure, ascites, and portal hypertension were consistently associated with poorer neurodevelopmental outcomes.

Conclusion: Children with BA are at increased risk of multidimensional neurodevelopmental impairment, particularly affecting motor and behavioral domains. Early identification and longitudinal neurodevelopmental surveillance are essential to optimize long-term functional outcomes in this vulnerable population.

Keyword: behaviour, biliary atresia, cognitive, motoric, neurodevelopment

Introduction

Biliary atresia (BA) is a rare but severe neonatal cholangiopathy characterized by progressive fibro-obliteration of the intrahepatic and extrahepatic bile ducts, leading to cholestasis and biliary cirrhosis early in life. Its incidence varies geographically, affecting approximately 1 in 15,000–20,000 live births in Europe, the United Kingdom, and North America, and up to 1 in 5,000–10,000 in East Asia.[1] Kasai portoenterostomy (KPE) remains the first-line surgical intervention, aiming to reestablish bile flow and delay progression to end-stage liver disease.[2] Although early KPE can slow hepatic fibrosis and improve short-term outcomes, more than half of affected children ultimately require liver transplantation, frequently within the first five years of life.[3] Advances in screening, surgical timing, and perioperative management have nonetheless resulted in substantial improvements in survival.

Improved survival has led to a growing cohort of children with BA who reach later childhood and adolescence, either with their native liver or following transplantation.[4] Consequently, clinical priorities have shifted from survival alone to long-term morbidity and health-related quality of life. Neurodevelopmental outcomes have emerged as a particularly important concern, given their relevance to cognitive functioning, educational attainment, and psychosocial adaptation.[5] The etiopathogenesis of BA is multifactorial and incompletely understood, involving genetic susceptibility and prenatal or perinatal insults that provoke immune-mediated bile duct injury.[6] Persistent cholestasis exposes the developing brain to prolonged metabolic stress, systemic inflammation, and bile acid dysregulation, while malabsorption of fat-soluble vitamins may further compromise neuromuscular and neurological development. In addition, complications of chronic liver disease, including growth failure, portal hypertension, recurrent infections, and prolonged hospitalization, may disrupt critical periods of neurodevelopment.[7]

Neurodevelopment is a multidimensional construct encompassing cognitive, motor, language, behavioral, and adaptive domains, all of which are essential determinants of long-term functional outcomes.[8] Despite growing interest in this area, the existing literature is fragmented and methodologically heterogeneous, with inconsistent evaluation of neurodevelopmental domains and wide variation in follow-up duration and outcome measures.[9]

To date, comprehensive syntheses integrating evidence across neurodevelopmental domains in children with BA remain limited. Therefore, this systematic review aims to critically appraise and synthesize the available evidence on neurodevelopmental outcomes in children with BA, identify domains most susceptible to impairment, and explore clinical factors associated with adverse developmental trajectories. Such data are essential to inform standardized neurodevelopmental surveillance and targeted early interventions in this vulnerable population.

Method

Review Design

This systematic review was designed and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The review protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD420251173999).

Eligibility Criteria

Studies were eligible for inclusion if they fulfilled the following predefined criteria: (1) involved pediatric participants (≤18 years of age) with a confirmed diagnosis of BA, including children surviving with their native liver, both with and without prior KPE, or with KPE performed within the first two years of life; (2) reported quantitative or qualitative assessments of neurodevelopmental outcomes, including cognitive, motor, language, behavioral, or psychosocial domains, measured using validated developmental or neuropsychological assessment tools; (3) adopted observational (prospective or retrospective cohort, case–control, or cross-sectional) or interventional study designs; and (4) were published as full-length articles in peer-reviewed journals. Studies were excluded if they consisted of case reports, small case series (<5 participants), narrative or systematic reviews, editorials, letters to the editor, conference abstracts, animal or in vitro studies. Furthermore, studies enrolling heterogeneous pediatric liver disease populations without stratified or extractable data specific to BA, or those lacking explicit reporting of neurodevelopmental outcomes, were excluded.

Timing of Neurodevelopmental Assessment

Neurodevelopmental assessments were conducted across a broad age range, reflecting the developmental domains evaluated in the included studies. Motor development was assessed primarily during infancy and early childhood, with evaluations performed from as early as 3 months of age and extending up to 22 years in studies reporting long-term motor outcomes. In contrast, assessments of neurocognitive and behavioral domains were conducted at later developmental stages, with evaluations performed in children aged 3 to 17 years, corresponding to periods when cognitive abilities and behavioral characteristics can be reliably measured using age-appropriate, standardized assessment tools. This age-specific approach aligns with established developmental trajectories and ensures appropriate interpretation of domain-specific outcomes.

Information Sources and Search strategy

A comprehensive and systematic literature search was conducted across the PubMed, Scopus, and Wiley databases to identify relevant studies. All articles published from database inception up to October 17, 2025, were considered. The search strategy combined controlled vocabulary and free-text terms related to biliary atresia ("biliary

atresia" OR "extrahepatic biliary atresia"), neurodevelopmental outcomes ("neurodevelopmental outcome" OR "neurocognitive" OR "psychomotor development" OR "brain development" OR "neurobehavioral" OR "developmental delay"), and pediatric populations ("infant" OR "newborn" OR "child" OR "pediatric"). The search was restricted to full-text articles published in the English language.

Study Selection and Data Extraction

All records identified through the database searches were imported into a reference management software, and duplicate entries were removed prior to screening. Two reviewers independently screened the titles and abstracts for eligibility based on the predefined inclusion and exclusion criteria. Full-text articles were subsequently retrieved and independently assessed for final inclusion. Any discrepancies between reviewers at each stage of the selection process were resolved through discussion, and when consensus could not be reached, a third reviewer was consulted. Data extraction was independently performed by two reviewers using a standardized and pilot-tested data extraction form. Extracted data included study characteristics (first author, year of publication, country, and study design), participant characteristics (sample size, age at assessment, birth weight, and gestational age), neurodevelopmental assessment tools, and key neurodevelopmental outcomes. Any disagreements in data extraction were resolved by consensus to ensure accuracy and completeness of the collected data.

Quality Assessment

The risk of bias of the included studies was independently evaluated by two reviewers using validated assessment tools according to study design. Cohort and case–control studies were assessed using the Newcastle–Ottawa Scale (NOS), whereas cross-sectional studies were evaluated using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies. The assessment encompassed key methodological domains, including participant selection, exposure and outcome measurement, confounding control, and completeness of data. Any disagreements between reviewers were resolved through discussion or, when necessary, consultation with a third reviewer. The overall risk of bias was summarized narratively and taken into account in the interpretation of the review findings.

Data Analysis

Due to substantial clinical and methodological heterogeneity among the included studies, a quantitative meta-analysis was not performed. Instead, a structured narrative synthesis was conducted. Neurodevelopmental outcomes were categorized into cognitive, motor, and behavioral domains, findings were descriptively synthesized with attention to the direction and consistency of effects. Where relevant, key clinical factors, including age at diagnosis, timing of intervention, and treatment modality, were considered to support an integrated interpretation of the evidence.

Result

Study Selection and Identification

The systematic literature search identified a total of 316 records from PubMed (n = 42), Scopus (n = 75), and Wiley (n = 199). After removal of 24 duplicate records, 292 articles remained for title and abstract screening, of which 279 were excluded for irrelevance. Ten full-text reports were sought for retrieval, and nine were successfully assessed for eligibility. Following full-text evaluation, two studies were excluded due to irrelevant clinical data. Ultimately, seven studies met the predefined inclusion criteria and were included in the final systematic review. The study selection process is summarized in the PRISMA flow diagram **(Figure 1)**.

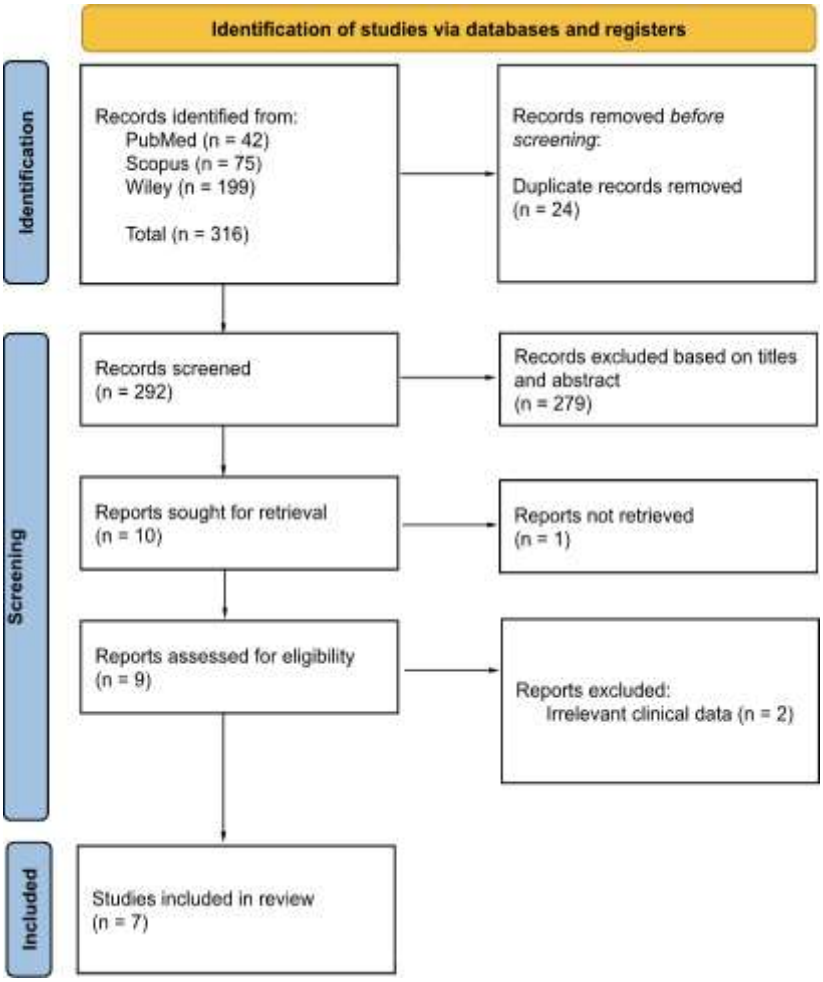

Figure 1. Diagram PRISMA Flow of Searching Strategies

Quality Assessment

Table 1 and Table 2 presents the risk of bias assessment using NOS for cohort studies and the JBI tool for cross-sectional studies. None of the cohort studies incorporated a control or comparison group, resulting in a maximum score of three

points in the NOS selection domain; one study was not awarded a score in this domain due to inadequate follow-up. Additionally, two cross-sectional studies did not sufficiently identify or control for potential confounding factors. Overall, five studies were judged to have a low risk of bias, while two cross-sectional studies were considered to have a moderate risk of bias.

Table 1. Risk of bias of the cohort study included

Study	Selection				Comparability	Outcome			Risk of Bias
	1	2	3	4	5	6	7	8	
Ng et al., 2018[10]	*	-	*	*	**	*	*	-	Low risk
Squires et al., 2020[11]	*	-	*	*	**	*	*	*	Low risk
Rodijk eta l., 2021[12]	*	-	*	*	*	*	-	*	Low risk
Dibbits et al., 2023[13]	*	-	*	*	*	*	*	*	Low risk

1. Representativeness of the exposed cohort
2. Selection of the non-exposed cohort
3. Ascertainment of exposure
4. Demonstration that outcome of interest was not present at start of study
5. Comparability of cohorts on the basis of the design or analysis controlled for confounders
6. Assessment of outcome
7. Was follow-up long enough for outcomes to occur?
8. Adequacy of follow-up of cohorts

Table 2. Risk of bias of the cross-sectional study included

Study	JBI Critical Appraisal Checklist								Risk of Bias
	1	2	3	4	5	6	7	8	
Rodijk et al., 2020[14]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Moderate risk
Ruuska et al., 2021[15]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low risk
Earl et al., 2025[16]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Moderate risk

1. Were the criteria for inclusion in the sample clearly defined?
2. Were the study subjects and the setting described in detail?
3. Was the exposure measured in a valid and reliable way?
4. Were objective, standard criteria used for measurement of the condition?
5. Were confounding factors identified?
6. Were strategies to deal with confounding factors stated?
7. Were the outcomes measured in a valid and reliable way?
8. Was appropriate statistical analysis used?

Summaries of Included Studies

Seven studies published between 2018 and 2025 were included in this systematic review, comprising four prospective cohort studies and three cross-sectional studies conducted across Europe and the United States.[10-16] Sample sizes ranged from 35 to

148 participants, encompassing infants, children, and adolescents with BA. Neurodevelopmental outcomes were assessed across multiple age groups, from early infancy to young adulthood, using validated and age-appropriate instruments, including the Bayley Scales of Infant and Toddler Development (BSID), Wechsler Intelligence Scales (WISC), General Movement Assessment (GMA), and standardized motor and adaptive behavior assessments. The primary objectives of the included studies were to characterize neurodevelopmental status in children with BA and to examine associations with clinical and disease-related factors, such as early neurological markers and long-term native liver survival. Collectively, the studies provided a comprehensive evaluation of cognitive, motor, language, and behavioral outcomes across different developmental stages. The key characteristics of the included studies are summarized in **Table 3.**

Table 3. Summaries of characteristics included studies

No	Author	Study Design & Location	Number of Participant (Age)	Birth weight, kg	Gestational age at birth	Assessment Tools	Key Findings
1	Earl et al., 2025[16]	Cross sectional (UK)	107 (<5 years old)	3.13 (1.04 - 4 .28)	39.00 (32.86 - 42.00)	MSEL, VABS, ADOS-2	• Parental concerns regarding neurodevelopment were reported in 37% of children, and 47% required at least one supportive service. • Children with BA under 5 years of age demonstrated significantly lower adaptive and cognitive scores than reference cohorts (P<.001). • ASD was identified in approximately 30% of children older than two years. • Earlier surgery and faster postoperative jaundice clearance were associated with better overall neurodevelopmental outcomes but not with autistic traits.

No	Author	Study Design & Location	Number of Participant (Age)	Birth weight, kg	Gestational age at birth	Assessment Tools	Key Findings
2	Dibbits et al., 2023[13]	Prospective Cohort (Netherlands)	41 (<3 years old)	3384 ± 470 gr	39 (IQR 36-42)	GMA, BSID-III	• Neurodevelopmental assessment in 38 toddlers with BA (mean age 29 ± 5 months; 70% post liver transplantation) showed below-average motor and cognitive performance in 39% and 17% of patients, respectively. • Abnormal GMA after KPE accurately predicted later motor and cognitive impairment, demonstrating high sensitivity (91% and 80%) and negative predictive value (94% for both). • These results suggest that motor impairment affects nearly one-third of toddlers with BA and that post KPE, GMA is a robust early predictor of neurodevelopmental risk
3	Rodijk et al., 2021[12]	Prospective Cohort (Netherlands)	35	3370 (IQR 2015 - 4285)	41 (IQR 36-42)	GMA	• Among 35 infants with BA assessed at diagnosis, atypical general movements were observed in 46%, a significantly higher prevalence than in healthy reference infants ($P < 0.001$). • No significant associations were found between atypical movements and clinical, biochemical, or anthropometric variables. • These results suggest early neurological vulnerability in infants with BA, supporting the need for close neurodevelopmental follow-up

No	Author	Study Design & Location	Number of Participant (Age)	Birth weight, kg	Gestational age at birth	Assessment Tools	Key Findings
4	Rodijk et al., 2020[14]	Cross sectional (Netherlands)	46 (6 –12 years old)	NR	39 (IQR 30-42)	WISC-III	• In a cohort of 46 school-aged children with BA (median age 11 years; 78% post–LT), 26% required special education, a rate significantly higher than the norm population (P < .01). • Motor performance and cognitive function were markedly impaired compared with population norms, with half of the children demonstrating low motor scores and a lower mean total IQ (91 vs 100; P < .01). • Neurodevelopmental outcomes did not differ between children with native livers and those who had undergone LT, indicating persistent impairments irrespective of transplant status.
5	Ruuska et al., 2021[15]	Cross sectional (Finland)	39 (1 – 20 years old)	3.270 ± 0.510	39 ± 1.7	BSID-III, WPPSI-III, WISC-IV, WAIS-IV	• Among 39 children with BA, mean total IQ was significantly below normative values (91 ± 15 vs 100 ± 15; P < 0.01), with earlier clearance of jaundice (< 0.05). • Motor development was impaired or at risk in 43% of assessed participants, and caregivers reported frequent functional difficulties in daily activities. • Neurodevelopmental outcomes did not differ significantly between children with native livers and those who had undergone LT

No	Author	Study Design & Location	Number of Participant (Age)	Birth weight, kg	Gestational age at birth	Assessment Tools	Key Findings
6	Squires et al., 2020[11]	Prospective Cohort (US)	93 (3 –12 years old)	NR	NR	WPPSI-III, WISC-IV	• In 93 children with BA and native liver, cognitive test scores on WPPSI III and WISC-IV were significantly higher than population norms across full-scale IQ and multiple domain indices. • Parental educational level was a strong positive predictor of full-scale IQ, whereas male sex and elevated bilirubin and GGT levels were associated with lower preschool IQ, and portal hypertension predicted reduced school-age IQ. • Overall, neurodevelopmental delay was not more prevalent in this cohort, although markers of advanced liver disease identified a vulnerable subgroup at risk for poorer cognitive outcomes.
7	Ng et al., 2018[10]	Prospective Cohort (US)	148 (1 –2 years old)	NR	NR	BSID-II, BSID-III	• In 148 children with BA assessed using BSID-III, neurodevelopmental scores at 12 and 24 months were significantly below normative values. • Ascites, growth faltering, and unsuccessful hepatoportoenterostomy independently predicted motor and cognitive language impairment, with failed surgery increasing risk more than fourfold at 2 years. • These results highlight early neurodevelopmental vulnerability in BA, particularly in those with advanced liver disease or poor growth.

MSEL = Mullens Scale of Early Learning; VABS = Vineland Adaptive Behavioral Scale; ADOS-2 = Autism Diagnostic Observation Schedule; BA = Biliary Atresia; ASD = Autism Spectrum Disorder; BSID-III = Bayley Scales of Infant Development, 3th edition; GMA = Prechtl's General Movement Assessment; KPE

= Kasai portoenterostomy; WISC-III = Wechsler Intelligence Scale for Children, third edition; WPPSI-III = The Wechsler Preschool and Primary Scale of Intelligence, 3rd edition; LT = liver transplantation; IQ = Intelligence Quotient; WISC-IV = Wechsler Intelligence Scale for Children, 4th edition; WAIS-IV = Wechsler Adult Intelligence Scale, 4th edition; GGT = Gamma-glutamyl transferase

Descriptive Analysis of Neurocognitive Domain

Across the included studies, neurocognitive outcomes in children with BA demonstrated heterogeneous patterns across developmental stages and assessment tools. In early childhood, infants with BA demonstrated significantly lower overall neurodevelopmental performance compared with reference populations, as reflected by reduced Early Learning Composite scores on the Mullen Scales of Early Learning, with the most pronounced deficits observed in expressive language and visual reception, and additional impairments in receptive language relative to low-likelihood reference cohorts.[15] Findings reported at toddler age were derived from separate cohorts and study populations, rather than longitudinal follow-up of the same children, and were assessed using different cognitive indices and methodological approaches, including comparisons against population normative cognitive scores with a mean or median value of 100. In these toddler cohorts, median cognitive index scores were not significantly different from normative population values.[13] However, a substantial proportion of children continued to demonstrate clinically meaningful impairment, with up to 17% scoring more than one standard deviation below the population mean. Taken together, these findings do not indicate resolution of early neurodevelopmental deficits but instead reflect methodological heterogeneity and differences in reference standards across studies.[13, 15]

In school-aged children and adolescents, several cross-sectional studies reported significantly lower mean total intelligence quotient (IQ) scores in BA patients compared with normative populations, particularly affecting performance-based indices and specific cognitive domains.[12] Consistent deficits were observed in attention, visuomotor integration, perceptual reasoning, planning, and inhibitory control, while verbal memory and strategy formation were relatively preserved.[10, 12] These findings were supported by age- and sex-adjusted analyses using standardized Wechsler scales, which demonstrated stable cognitive performance across age groups but persistent underperformance relative to population norms.[10]

Longitudinal cohort studies provide the most robust evidence for evaluating neurodevelopmental trajectories over time, as they allow assessment of cognitive outcomes within the same individuals and minimize bias related to cross-sectional comparisons. In this context, the reviewed longitudinal data indicate that children surviving with their native liver can achieve cognitive performance comparable to, or exceeding, standardized test norms across multiple domains, including full-scale IQ,

verbal abilities, perceptual reasoning, and processing speed.[14, 15] Notably, higher parental educational attainment consistently emerged as a significant positive predictor of cognitive outcomes, suggesting an important role of environmental and socioeconomic factors in shaping long-term neurodevelopment. Parental education may reflect differences in cognitive stimulation, health literacy, and access to supportive resources, which could partially mitigate the adverse neurodevelopmental impact of early-life liver disease. Conversely, male sex and markers of more advanced liver disease were associated with lower cognitive performance, underscoring the interplay between biological vulnerability and modifiable environmental influences. These findings highlight the importance of considering parental education when interpreting neurodevelopmental outcomes and designing follow-up and early intervention strategies in this population.[11, 13]

Finally, assessments conducted at 12 and 24 months using Bayley Scales indicated broadly reduced cognitive performance relative to test norms at one year of age, with effect sizes attenuating by two years, particularly among children assessed with the Bayley-III. Overall, the evidence suggests that while a subset of children with BA achieve age-appropriate cognitive outcomes, particularly in cohorts with favorable clinical profiles, BA is frequently associated with domain-specific cognitive vulnerabilities that may persist into later childhood.[11, 13, 15]

Descriptive Analysis of Motoric Domain

Motor development outcomes in children with BA were consistently reported as vulnerable across infancy, toddlerhood, and later childhood, although the magnitude and pattern of impairment varied by age and assessment method. In toddler cohorts, overall motor performance was significantly below population norms, with median total motor index scores indicating clinically meaningful delay. More than one-third of toddlers demonstrated motor impairment exceeding one standard deviation below the population mean, with gross motor skills disproportionately affected compared with fine motor skills.[15]

Early motor repertoire abnormalities were frequently identified at the time of BA diagnosis using General Movement Assessment. Among 35 infants younger than 3 months, 46% demonstrated atypical general movements, including abnormal writhing or fidgety patterns. This prevalence substantially exceeds that reported in normative populations. These findings suggest early disruption of motor system development, observable within the first months of life and prior to surgical intervention.[14]

In preschool-aged children, motor outcomes assessed using standardized motor batteries were significantly poorer than normative references across all domains, including fine motor skills, ball skills, and balance, with half of the children classified within the low-performance range. Similarly, among children and adolescents assessed

with the Movement Assessment Battery for Children, distributions of total motor scores differed significantly from test norms, with increased proportions of individuals classified as at risk for or meeting criteria for motor difficulties. Deficits were most prominent in manual dexterity and aiming and catching skills, while balance performance appeared relatively preserved. Motor performance did not differ significantly across age subgroups, suggesting persistence of motor difficulties over time.[13, 14]

Longitudinal cohort data further indicated that motor impairment in early childhood was associated with disease severity and clinical course. Older age at KPE, the presence of medical complications, impaired somatic growth, ascites, and unsuccessful surgical outcomes were identified as key risk factors for physical and motor delay, with unsuccessful portoenterostomy remaining a strong independent predictor of motor impairment at two years of age. The available evidence indicates that children with BA are at increased risk of early and persistent motor development difficulties, particularly affecting gross motor and coordination-related domains, with outcomes closely linked to early disease severity and postoperative clinical status.[11]

Descriptive Analysis of Behavioral Domain

Children with BA demonstrate increased vulnerability in behavioral and adaptive functioning across development. In infancy, Vineland Adaptive Behavior Scales assessments showed significantly lower adaptive composite scores compared with reference cohorts, particularly in communication, socialization, and motor domains, with additional deficits in daily living skills. Autism-related behaviors were frequently observed early, with nearly half of assessed infants exceeding Autism Diagnostic Observation Schedule–2 thresholds and approximately one-third meeting criteria for a clinical or research diagnosis of autism spectrum disorder, showing a male predominance. During toddlerhood and later childhood, behavioral difficulties were identified in a subset of children, primarily affecting overall behavior, attention, and hyperactivity, as assessed using the Vineland Adaptive Behavior Scales (VABS). Additional parent-reported outcomes derived from standardized questionnaires, including the Five-to-Fifteen-Revised (5–15R) and the Child Behavior Checklist (CBCL 1.5–5), suggested increased difficulties in executive functioning, memory, learning, and language domains, whereas impairments in social and emotional functioning were reported less consistently. Formal psychiatric diagnoses were infrequently documented. However, a small number of children were reported to have a clinical diagnosis of attention-deficit/hyperactivity disorder.[16] Overall, behavioral and adaptive difficulties in children with BA appear early and may persist into later childhood, with variability across domains and individuals.[14, 16]

Discussion

This systematic review provides an updated and domain-specific synthesis of neurodevelopmental outcomes in children with BA, a rare neonatal cholangiopathy in which improving survival has shifted clinical focus toward long-term morbidity. Importantly, previous systematic or narrative reviews in BA were limited by inclusion of older cohorts, lack of recently published studies, and a predominant focus on global cognitive outcomes, without specific evaluation of motor, behavioral, and autism-related domains. By incorporating recent studies published up to 2025 and explicitly examining cognitive, motor, and behavioral outcomes, including autism spectrum-related features, this review addresses a critical gap in the literature. Overall, the findings demonstrate that children with BA are at increased risk of neurodevelopmental impairment across multiple domains, with motor dysfunction emerging as the most consistent and early abnormality, and behavioral and adaptive difficulties frequently evident from infancy.

The results are consistent with earlier reports in BA and other pediatric chronic liver diseases, which describe heterogeneous cognitive outcomes and persistent motor and executive function deficits. However, unlike prior reviews, this synthesis highlights that neurodevelopmental vulnerability in BA is not limited to cognition alone.[17, 18] Early motor abnormalities detected using GMA were prevalent even at diagnosis, and behavioral phenotypes, including attention difficulties and increased autism spectrum traits were identified in early childhood.[19] While early KPE and effective bile drainage were associated with more favorable cognitive outcomes, impairments were observed in both native-liver and post-transplant cohorts, suggesting that transplantation does not fully reverse early neurodevelopmental insults.[20] These findings extend previous knowledge by clarifying domain-specific risks and their persistence across developmental stages.

The associations between neurodevelopmental outcomes and markers of advanced liver disease support biologically plausible mechanisms.[21] Prolonged cholestasis, systemic inflammation, malnutrition, and fat-soluble vitamin deficiencies may disrupt neurogenesis, myelination, and synaptic maturation during critical periods of brain development.[7, 21] Early surgical intervention and optimized postoperative care may reduce, but not abolish, these effects by limiting metabolic and inflammatory exposure. Notably, none of the included studies reported neurodevelopmental harm attributable to surgical or medical treatment, reinforcing the interpretation that disease severity and chronicity, rather than intervention-related toxicity, drive adverse outcomes.[22]

Beyond cognitive and motor impairment, this review identifies behavioral and adaptive dysfunction as clinically relevant but previously underrecognized aspects of BA. Elevated rates of attention problems, executive dysfunction, and autism spectrum

disorder–related behaviors suggest early alterations in social–communication and self-regulatory development.[5] Parental educational attainment consistently emerged as a positive predictor of cognitive outcomes, highlighting the moderating role of environmental and socioeconomic factors.[21, 22] Clinically, these findings support the need for standardized, longitudinal neurodevelopmental surveillance in children with BA, with particular attention to early motor assessment and behavioral screening to enable timely referral for targeted intervention.[20]

This review is strengthened by adherence to PRISMA guidelines, prospective protocol registration, comprehensive literature searching, and the inclusion of recent studies employing validated behavioral, cognitive, and motor assessment tools. Importantly, a key strength lies in the integrated evaluation of behavioral outcomes, including autism-related features, across different developmental stages. Several limitations should be acknowledged. First, the literature search was restricted to English-language publications, which may have led to the exclusion of relevant studies published in other languages and introduced potential language bias. Although the databases searched are widely used and encompass a broad range of international journals, this restriction may limit the completeness and generalizability of the findings. Additional limitations include heterogeneity in study designs and outcome measures, modest sample sizes, limited use of control groups, and a predominance of data from high-income settings.

Furthermore, all included studies were observational in nature, rendering the findings susceptible to confounding and selection bias and limiting causal inference regarding the relationship between BA and neurodevelopmental outcomes. Future randomized or interventional studies, where feasible, may provide stronger evidence to clarify the effects of clinical and supportive interventions on long-term neurodevelopment. Despite these constraints, the overall consistency of findings across multiple developmental domains supports the conclusion that BA is associated with significant and multidimensional neurodevelopmental risk, underscoring the need for early and longitudinal developmental monitoring as part of standard clinical care.

Conclusion

This systematic review demonstrates that BA is associated with significant and multifaceted neurodevelopmental vulnerability, with motor and behavioral impairments emerging early and frequently persisting into later childhood, while cognitive outcomes remain heterogeneous. Disease severity and postoperative clinical courses consistently influence developmental trajectories, underscoring the importance of early surgical success and optimized medical management. Future research should prioritize large, multicenter longitudinal studies with standardized, domain-specific neurodevelopmental assessments, particularly focusing on behavioral and autism-related outcomes. Additionally, interventional studies evaluating the

effectiveness of early developmental and psychosocial support programs are needed to determine strategies that may improve long-term neurodevelopmental outcomes in children with BA.

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Conflict of Interest

The authors declare no conflict of interest.

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Original Article

The Correlation Between Low Milk Supply in Breastfeeding and The Severity of Neonatal Hyperbilirubinemia

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Abstract:

Background: Inadequate breastfeeding can cause neonatal hyperbilirubinemia. Hyperbilirubinemia was the fifth leading cause of neonatal mortality in Indonesia with a prevalence of approximately 5.6%. The severe level of bilirubin concentration can cause life- threatening kernicterus. The study aimed to examine the correlation between low milk supply in breastfeeding and the severity of neonatal hyperbilirubinemia among newborns who were admitted to Assyifa Mother and Child Hospital in Tangerang, Banten.

Methods: A cross-sectional study was conducted on 20 neonates diagnosed with unspecified hyperbilirubinemia who were referred to either Emergency Department or Pediatric Department in Assyifa Mother and Child Hospital. Data were obtained from electronic medical records, including information related to mothers and neonates. Data on breast milk supply in breastfeeding mothers were obtained from patient anamnesis records. Statistical analysis was performed using the Fisher's test with SPSS version 30.

Result: Hyperbilirubinemia severity was categorized into three severity levels: level 1 (12-18 mg/dL), level 2 (19-24 mg/dL), level 3 (25-30 mg/dL). There were 8 neonates with adequate breastmilk supply that categorized who were classified into level 2. In contrast, 12 neonates with inadequate breastmilk supply were classified into levels 2 and 3. A significant correlation was found between inadequate breastmilk supply and increased severity of neonatal hyperbilirubinemia ($p = 0.042$). Higher severity of hyperbilirubinemia was associated with lower quantities of breastfeeding.

Conclusion: The study shows a significant correlation between inadequate breastmilk supply in breastfeeding and the severity of neonatal hyperbilirubinemia.

Keyword: breastfeeding, breastmilk supply, neonatal hyperbilirubinemia, severity of hyperbilirubinemia

Introduction

According to the 2023 Indonesian Basic Health Research and Ministry of Health of The Republic of Indonesia Survey (Kemenkes), hyperbilirubinemia was the fifth leading cause of neonatal mortality in Indonesia, with an overall prevalence of 51,47% among neonates. The prevalence is higher in preterm infants (around 58%) compared to term infants (around 50%).[1] Severe hyperbilirubinemia may progress to kernicterus, a permanent and life-threatening neurological condition. Several contributing factors have been identified, including blood group incompatibility, prematurity, sepsis, postnatal weight loss, inadequate feeding, and a family history of jaundice.[1, 2] Previous reports indicated that unconjugated bilirubin levels exceed 12.9 mg/dL in 6–7% of neonates with physiological jaundice, while nearly 3% present with levels above 15 mg/dL.[2, 3]

Neonatal hyperbilirubinemia is classified into physiological or pathological jaundice. Physiological jaundice is a benign, self-limiting condition characterized by a rise in total serum. bilirubin, which typically peaks at 5–12 mg/dL on days 3–5 of life and resolves within 1–2 weeks.[1, 4] Breastfeeding jaundice usually arises during the first week of life and is caused by insufficient breast milk intake, which leads to dehydration, increased enterohepatic circulation, and reduced bilirubin clearance.[3-5] Another example is breastmilk jaundice, which develops after the first week of life due to inhibitory substances in breast milk that delay bilirubin conjugation.[4]

Low milk supply plays a central role in the development of breastfeeding jaundice. It may occur due to maternal factors such as delayed onset of lactogenesis II, poor latch or ineffective sucking, primiparity, caesarean delivery, or maternal illness.[6-8]Inadequate milk intake is reflected in persistent infant hunger, reduced urine and stool output, excessive weight loss, and rising bilirubin levels. Without intervention, these conditions can lead to severe hyperbilirubinemia and, in some cases, kernicterus.[6, 9]

Early recognition and management of breastfeeding difficulties are therefore critical. Failure to address low milk supply before hospital discharge increases the risk of dehydration and bilirubin encephalopathy.[7, 9] Professional guidelines recommend that newborns breastfeed 8–12 times daily during the early neonatal period to ensure adequate intake and reduce the risk of jaundice. Providing timely breastfeeding education, rooming-in practices, and lactation support can significantly improve milk supply and reduce complications.

This study focuses on breastfeeding jaundice by examining the relationship between low milk supply and the severity of neonatal hyperbilirubinemia. By identifying low milk supply as a modifiable risk factor, this research aims to support the development of targeted breastfeeding support and clinical monitoring strategies to reduce the burden of severe neonatal hyperbilirubinemia.

Method

Study Design and Data Collection

A cross-sectional study was conducted between March to June 2025 involving 20 neonates with unspecified hyperbilirubinemia who were referred to the Emergency Department or the Department of Paediatric at Assyifa Mother and Child Hospital. Eligible participants were neonates aged 0–28 days diagnosed with neonatal jaundice (ICD-10 code P59.9) during the study period. Infants were excluded if their parents declined to provide informed consent or if hyperbilirubinemia was attributed to a specific underlying cause such as hemolytic disease, sepsis, or metabolic disorder.

Data were collected from electronic medical record**,** which contained demographic and clinical information of both mothers and infants. Maternal and neonatal anamnesis records were reviewed to obtain data on feeding practices and breast milk supply.

Variables and Operational Definitions

The dependent variable was the severity of neonatal hyperbilirubinemia, determined by total serum bilirubin (TSB) levels measured using standardized laboratory assays. Hyperbilirubinemia was operationally defined as a TSB level ≥12 mg/dL within the first 28 days of life. For analytical purposes, TSB values were stratified into three categories: Mild = Level 1 (12–18 mg/dL), Moderate = Level 2 (19–24 mg/dL), and Severe = Level 3 (25–30 mg/dL). These ranges were adapted from bilirubin level distributions reported in observational studies, including Hassan et al., to reflect increasing degrees of biochemical severity and to facilitate statistical comparison between study groups.[2] However, these categories were defined by the authors for research analysis and do not represent standardized clinical severity classifications. Current recommendations from the American Academy of Pediatrics (AAP) emphasize risk assessment and treatment decisions based on hour-specific bilirubin nomograms adjusted for gestational age and neurotoxicity risk factors rather than fixed TSB cutoff ranges. Accordingly, the severity groupings in this study should be interpreted as analytical stratifications rather than guideline-based clinical severity categories.[10, 11]

The independent variable was low milk supply in breastfeeding mothers, which was defined as maternal perception of insufficient breast milk production, indicated by persistent infant hunger after breastfeeding or the need for early formula supplementation. This information was obtained through maternal interviews and confirmed with feeding records in the medical charts.

Feeding practices were categorized into three categories: exclusive breastfeeding (infants receiving only breast milk without supplementation), formula feeding (infants receiving only commercially prepared formula), and mixed feeding (infants receiving

both breast milk and formula). Breastfeeding frequency was classified as adequate if breastfeeding occurred ≥ 8 times per 24 hours and inadequate if < 8 times, based on maternal report. This classification was based on the assumption that neonates aged 0-3 days are typically breastfed approximately eight times per day or receive an intake equivalent to 60 mL/Kg/day, increasing to approximately 120 mL/Kg/day during the first weeks of life.[10] Demographic variables included age (in completed days), sex (as recorded in medical charts), and birth weight. Birth weight was measured in grams at delivery and categorized into low birth weight (< 2500 g) and normal birth weight (≥ 2500 g).

Data Analysis

Hyperbilirubinemia severity and total serum bilirubin were compared across these groups. Infants were grouped according to feeding method (exclusive breastfeeding, formula feeding, or mixed feeding) and breastfeeding frequency (adequate or inadequate). Bilirubin levels were compared across these groups. All data were verified against patient records prior to analysis. Statistical analysis was performed using SPSS version 30. After testing for normality, the Fisher's test was used to assess associations between categorical variables. A p- value of < 0.05 was considered statistically significant.

Ethical Approval

Ethical approval for this study was obtained from the Ethics Committee of Assyifa Mother and Child Hospital with The Ethical Number: No. 498/SKT-RSIAA/X/2025. Written informed consent was obtained from the parents or legal guardians of all participating infants prior to data collection.

Result

The demographic and feeding characteristics of neonates with hyperbilirubinemia are summarized in **Table 1.** The study population consisted predominantly of female neonates, with most neonates delivered via caesarean section. Neonates were assessed during the early neonatal period, and birth weight as well as feeding frequency were generally within expected neonatal ranges. Variations in type of milk feeding practices were observed, including exclusive breastfeeding, formula feeding, and mixed feeding.

Table 2 summarizes the relationship between breastfeeding adequacy and serum bilirubin levels in neonates with hyperbilirubinemia. Adequate breastfeeding was observed in 40% (n = 8) of infants, all of whom presented with moderate hyperbilirubinemia (Level 2). In contrast, among neonates with inadequate breastfeeding (n = 12), 50% demonstrated progression to severe hyperbilirubinemia (Level 3).

Table 1. Demographic and feeding characteristics data of neonates with hyperbilirubinemia.

Variables	Values n (%)	Mean ± SD
Age (days)	–	8.9 ± 4.5
Gender		
Male	8 (40.0)	–
Female	12 (60.0)	–
Method of delivery		
Caesarean section	17 (85.0)	–
Pervaginam	3 (15.0)	–
Birth weight (g)	–	3,092 ± 359.18
Feeding frequency (times/day)	–	7.50 ± 2.56
Types of milk feeding		
Breastmilk	8 (40.0)	–
Formula feeding	4 (20.0)	–
Mixed feeding	8 (40.0)	–

A statistically significant association was found between breastfeeding adequacy and bilirubin severity (p = 0.042). Furthermore, neonates with inadequate breastfeeding had a twofold increased risk of developing severe hyperbilirubinemia compared with those receiving adequate breastfeeding (RR = 2.00; 95% confidence interval (CI), 1.36–3.52).

Table 2. Association between breastfeeding adequacy and hyperbilirubinemia severity in neonates with hyperbilirubinemia (n =20)

Breastfeeding Adequacy	Hyperbilirubinemia Severity		Risk Ratio	95% CI	p-value
	Level 2 n (%)	Level 3 n (%)			
Adequate Breastfeeding (n=8)	8 (100.0 %)	0 (0.0%)	2.00	1.36 - 3.52	0.042
Inadequate Breastfeeding (n=12)	6 (50.0%)	6 (50.0%)			

CI = Confidence Interval

Breastfeeding adequacy characteristics

Further analysis of the adequate breastfeeding group demonstrated variability in feeding practices within this category. Among neonates classified as having adequate breastfeeding, five neonates received exclusive breast milk feeding, three received mixed feeding, and none were exclusively formula-fed. These findings indicate that adequate breastfeeding in this study population was predominantly achieved through exclusive

breastfeeding, with a smaller proportion supported by combined breast milk and formula feeding.

Table 3 shows the analysis of brestfeeding frequency in relation to total serum bilirubin levels among neonates who were fed ≤8 times per day exhibited higher mean bilirubin concentrations compared with those feeding ≥ 8 times per day (mean 21.4 ± 4.1 mg/dL vs mean 18.5 ± 1.6 mg/dL). Although this difference did not reach statistical significance (Mann-Whitney test, p=0.667), the observed trend suggests that lower breastfeeding frequency may be associated with higher bilirubin levels. Taken together, these findings underscore the potential role of adequate and frequent breastfeeding in reducing the severity of neonatal hyperbilirubinemia.

Table 3. Association between breastfeeding frequency and total serum bilirubin

Breastfeeding Frequency	Total Serum Bilirubin (mg/dL)	p-value
< 8 times / day	21.4 ± 4.1	0.667
≥ 8 times / day	18.5 ± 1.6	

The association between demographic characteristics and the severity of neonatal hyperbilirubinemia is presented in **Table 4.** No statistically significant associations were observed between hyperbilirubinemia severity and sex, method of delivery, enteral feeding type, or breastfeeding frequency (all p > 0.05).

Table 4. The Association between demographic characteristics and hyperbilirubinemia severity

Characteristics	Category	Level 2 n (%)	Level 3 n (%)	p-value
Gender	Male	5 (62.5)	3 (37.5)	0.642
	Female	9 (75)	3 (25)	
Method of delivery	Caesarean section	9 (75)	5 (29.4)	0.898
	Pervaginam	2 (66.7)	1(33.3)	
Type of milk feeding	Breastmilk	7(87.5)	1(12.5)	0.077
	Formula	1(25)	3 (75)	
	Mixed feeding	6 (75)	2(25)	
Breastfeeding/day	< 8 times	6 (75)	5 (50)	0.141
	≥ 8 times	9 (90)	1 (10)	

Discussion

This study demonstrates a significant association between inadequate breastfeeding intake and increased severity of neonatal hyperbilirubinemia. Among the 20 neonates included, 40% had adequate breastfeeding, while 60% were classified as having inadequate intake. Insufficient breastfeeding may result in dehydration and reduced caloric intake, leading to increased enterohepatic circulation and impaired bilirubin elimination. When combined with early postnatal discharge and delayed recognition

of feeding difficulties, these conditions may contribute to severe hyperbilirubinemia and, in extreme cases, kernicterus. Previous studies have shown that reduced caloric intake during the early neonatal period may promote lipolysis, increase circulating free fatty acids, and interfere with bilirubin conjugation, thereby exacerbating bilirubin accumulation.[4, 12]

It is important to distinguish breastfeeding jaundice from breast milk jaundice, as their underlying mechanisms and clinical implications differ. Breastfeeding jaundice primarily results from insufficient milk intake during the early neonatal period, whereas breast milk jaundice develops later and is associated with bioactive components in human milk that inhibit bilirubin conjugation, resulting in prolonged but generally benign hyperbilirubinemia.[5, 7] Although breastfeeding jaundice is classically described as occurring within the first week of life, this distinction should not rely solely on chronological age. In the present study, neonates presented at a mean age exceeding one week of life; however, classification as breastfeeding jaundice was based on documented feeding inadequacy rather than timing of presentation alone. Persistent ineffective latch, delayed lactogenesis, or unrecognized breastfeeding difficulties may prolong inadequate milk intake beyond the early neonatal period, thereby explaining the later clinical presentation observed in this cohort. These findings emphasize that differentiation between breastfeeding jaundice and breast milk jaundice requires comprehensive evaluation of feeding adequacy, hydration status, and clinical progression rather than age of onset alone.

Consistent with this interpretation, neonates fed fewer than eight times per day exhibited higher mean total serum bilirubin levels compared with those receiving eight or more daily feedings. This observation supports existing evidence that insufficient breastfeeding frequency contributes to breastfeeding jaundice. Current recommendations from the American Academy of Pediatrics advocate 8–12 feedings per day during the early neonatal period to ensure adequate milk intake and reduce the risk of hyperbilirubinemia.[9]

Regarding feeding type, formula-fed infants in this cohort appeared to demonstrate higher bilirubin levels compared with mixed-fed and exclusively breastfed infants. However, this finding should be interpreted cautiously. Early formula supplementation may reduce breastfeeding frequency and breast stimulation, potentially impairing maternal milk production. Alternatively, the observed association may reflect reverse causation, whereby infants with early or more severe jaundice were more likely to receive formula supplementation as part of clinical management rather than formula feeding being the primary cause of elevated bilirubin levels. This interpretation is supported by interventional studies demonstrating that appropriately timed formula supplementation in selected high-risk neonates may reduce bilirubin levels and prevent excessive postnatal weight loss.[2, 8]

Several confounding factors and group heterogeneity may also have influenced the observed findings. Neonates categorized according to feeding type may have differed in gestational age, perinatal characteristics, or timing of bilirubin measurement, all of which substantially affect bilirubin concentrations.[3, 6, 12] Misclassification bias may also have occurred, as some infants initially breastfed could have transitioned to formula feeding secondary to inadequate intake or worsening jaundice during hospitalization. Furthermore, important neonatal variables known to influence hyperbilirubinemia severity including gestational age, degree of postnatal weight loss, timing of bilirubin assessment in hours of life, and hemolytic conditions such as ABO or Rh incompatibility and glucose-6-phosphate dehydrogenase deficiency were not consistently documented in the medical records. Consequently, multivariable adjustment could not be performed, and residual confounding cannot be excluded.

The relatively small sample size further limits generalizability and may amplify the influence of individual variability. In addition, differences in the timing of bilirubin measurement may have affected group comparisons, as bilirubin trajectories vary according to feeding patterns.[4, 9] Therefore, these findings should be interpreted cautiously. Nevertheless, the results underscore the clinical importance of early recognition of breastfeeding inadequacy as a potentially modifiable risk factor. Careful feeding assessment, detailed breastfeeding history, and standardized bilirubin monitoring remain essential components of neonatal care. Larger prospective studies are required to confirm these associations and to clarify whether observed differences across feeding groups reflect true biological effects or methodological limitations.

Limitations

This study included 20 neonates, representing the total eligible population during the study period based on strict inclusion and exclusion criteria. Although this sample size is comparable to other neonatal hyperbilirubinemia studies, where recruitment is often limited by ethical considerations, strict diagnostic criteria, and case availability, the small sample size may limit the statistical power of the analysis. This limitation may also reduce the generalizability of the findings to broader neonatal populations. In addition, the exploratory cross-sectional design of this study allows only for the identification of associations and does not permit causal inference. Further studies with larger sample sizes and multicenter designs are needed to validate and extend these findings.

Potential Bias

This study may be subject to several potential sources of bias. First, the sample was limited to a single hospital and included only 20 infants, which may limit the generalizability of the findings. Second, data on breastfeeding frequency and breast milk supply were obtained through anamnesis and medical records, which may

introduce recall or reporting bias. Additionally, the clinical assessment using Kramer's criteria was performed during initial evaluation. However, the classification of hyperbilirubinemia severity for statistical analysis was determined exclusively using laboratory-measured TSB levels. These factors should be considered when interpreting the results.

Conclusion

This study demonstrated a statistically significant association between breastfeeding adequacy and total serum bilirubin levels among neonates with hyperbilirubinemia, with inadequate breastfeeding more frequently observed in infants with greater bilirubin severity. Nevertheless, these findings should be interpreted cautiously due to the small sample size, cross- sectional study design, use of author-defined bilirubin severity groupings, and the inability to adjust for important neonatal confounding variables.

Although the results highlight the potential contribution of adequate and frequent breastfeeding to neonatal outcomes, causal relationships cannot be established. Future research involving larger sample sizes and longer observation periods is required to better clarify temporal relationships between feeding adequacy and bilirubin progression. In addition, studies incorporating objective measurements of nutritional intake, such as caloric intake assessment, together with hour-specific bilirubin nomograms and gestational age–adjusted risk stratification recommended in current clinical guidelines, are needed to strengthen clinical applicability and external validity.

From a clinical perspective, early identification of breastfeeding difficulties and appropriate monitoring of bilirubin levels remain essential components of neonatal care. The provision of structured lactation support and careful post-discharge follow-up may help optimize feeding adequacy and potentially reduce the risk of elevated bilirubin levels in newborns.

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Conflict of Interest

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Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Case Report

Choledochal Cyst Todani Classification Type IC and Choledocholithiasis Presenting as Recurrent Pancreatitis in a 7-Year-Old Girl – A Case Report

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Abstract:

Background: Choledochal cyst is an uncommon but important cause of biliary pathology in the pediatric population which can lead to choledocholithiasis and recurrent pancreatitis. High clinical suspicion, comprehensive imaging, and multidisciplinary evaluation are essential for accurate diagnosis and treatment. Definitive management is achieved through surgical intervention.

***Case*:** A 7-year-old girl experienced recurrent postprandial right upper quadrant and epigastric pain for three years, with fluctuating pancreatic and hepatic enzymes. Initial ultrasound and magnetic resonance cholangiopancreatography (MRCP) revealed ductal dilatation with biliary sludge, while multislice computed tomography (MSCT) suggested autoimmune pancreatitis, leading to temporary steroid response. Symptoms persisted, and contrast-enhanced magnetic resonance imaging (MRI) demonstrated fusiform common bile duct dilatation with debris, confirming Todani type IC choledochal cyst and choledocholithiasis. She underwent laparoscopic cyst and gallbladder excision with Roux-en-Y hepaticojejunostomy. Intraoperative and histological findings verified sludge, gallstones, and chronic cholecystitis.

***Discussion*:** Choledochal cysts should be considered in pediatric recurrent pancreatitis, particularly with biliary obstruction. Advanced imaging and differential diagnosis are crucial. Surgical excision with biliary reconstruction is the treatment of choice.

Conclusion: Early recognition and timely surgical intervention are essential to prevent long-term complications.

Keywords: autoimmune pancreatitis, biliary obstruction, hepaticojejunostomy, laparoscopic surgery, magnetic resonance cholangiopancreatography

Introduction

Choledochal cysts (CCs) are uncommon congenital malformations of the biliary system, defined by segmental or diffuse dilatation of the intra- and/or extrahepatic bile ducts.[1] The Todani classification categorizes CCs, with type I being the most common (80–90% of cases).[2-4] Choledocholithiasis, the presence of stones within the common bile duct, often arises secondary to congenital biliary anomalies and may manifest as biliary colic, obstructive jaundice, or recurrent acute pancreatitis.[5, 6] Untreated CCs may lead to acute recurrent pancreatitis (ARP) through episodic obstruction at the pancreaticobiliary junction.[6] Recurrent pancreatitis in children poses substantial diagnostic complexity, necessitating evaluation for structural, genetic, metabolic, and immune-mediated etiologies.[7] Autoimmune pancreatitis (AIP) can mimic biliary causes, especially when imaging and antibody tests overlap.[8, 9]

We report a 7-year-old girl with a Todani type IC choledochal cyst complicated by choledocholithiasis, manifesting as recurrent pancreatitis and definitively treated via laparoscopic excision with Roux-en-Y hepaticojejunostomy. This case is unique because of the prolonged diagnostic course, autoimmune pancreatitis–like features, and delayed identification of a structural biliary cause in a resource-limited setting.

Case

A 7-year-old girl initially presented with acute postprandial pain in the right upper quadrant and epigastrium, associated with nausea, reduced appetite, and a low-grade fever, but without jaundice. Laboratory tests revealed marked pancreatic and hepatic enzyme elevations: amylase 233 U/L (reference 25–101 U/L), lipase 162.6 U/L (reference ~60 U/L), AST 536.2 U/L (reference <34 U/L), and ALT 410.4 U/L (reference <55 U/L). In this first episode, abdominal ultrasonography demonstrated acute pancreatitis accompanied by dilation of the pancreatic duct, proximal common bile duct, cystic duct, and intrahepatic biliary branches. Her symptoms resolved within a few days following conservative therapy. Three months later, she re-presented with similar abdominal pain and vomiting. Laboratory testing again showed elevation of hepatic and pancreatic markers: AST 295.6 U/L, ALT 460.9 U/L, Amylase 246.8 U/L, Lipase 162.4 U/L, and markedly elevated GGT 305.0 U/L (normal <33 U/L). Hepatitis B serology was non-reactive. She was diagnosed with acute recurrent pancreatitis (ARP) and improved with supportive care.

During the second year of illness, she developed her most severe biochemical flare, with Amylase 832 U/L and Lipase 1771 U/L (approximately 7–15× pediatric upper limits of normal), while bilirubin, alkaline phosphatase, and complete blood count were within pediatric reference ranges. Intermittent hair thinning was also reported. Because no structural abnormality had been detected previously despite multiple recurrences, AIP was considered. ANA IFA was positive at 1:100, fine-speckled; C3

was mildly elevated at 132.2 mg/dL (pediatric normal 90–180 mg/dL). A multislice computed tomography (MSCT) scan demonstrated features compatible with AIP. Given limited availability of autoimmune diagnostic assays in Bali, she was treated empirically with intravenous methylprednisolone 2 mg/kg/day, later transitioned to oral taper, along with weekly Methotrexate 10 mg/BSA. Symptoms initially improved, but after approximately three months she developed dyspepsia. Esophagogastroduodenoscopy revealed erosive fundal gastritis, prompting discontinuation of immunosuppressive therapy.

Shortly after cessation, abdominal pain recurred. Laboratory values again showed elevated pancreatic and hepatic markers: Amylase 433 U/L, Lipase 413 U/L, AST 229 U/L, and ALT 311 U/L. Because of an incomplete steroid response and continued episodes, further structural evaluation was pursued. High-resolution abdominal magnetic resonance imaging (MRI) was obtained and findings were consistent with a Todani type I-C choledochal cyst with upstream biliary stasis due to distal obstruction **(Figure 1A–B)**. These MRI findings established a clear anatomic cause, a choledochal cyst and choledocolithiasis, for her recurrent pancreaticobiliary obstruction.

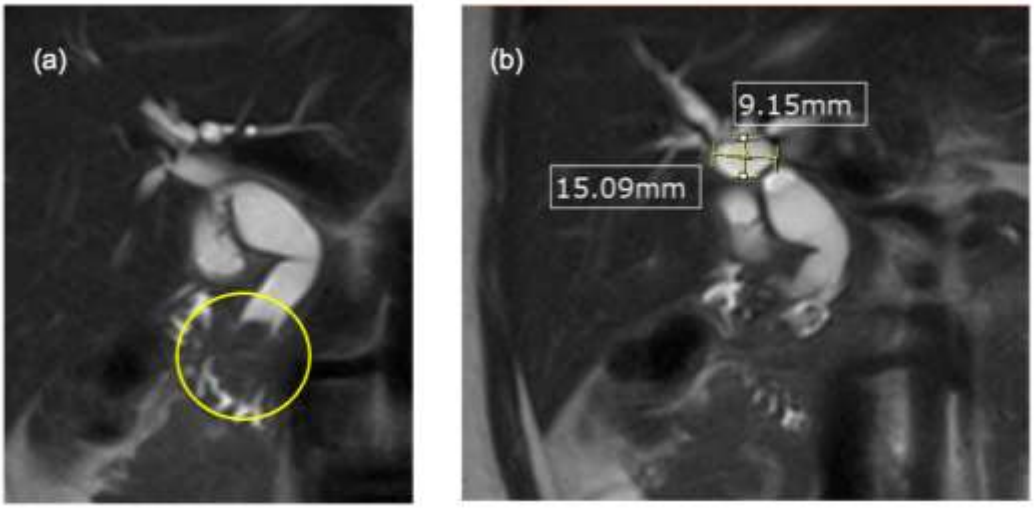

Figure 1. Contrast-enhanced abdominal MRI

a) Suspected choledocholithiasis on the distal common bile duct with dilated left and right intrahepatic duct, common hepaticus communis and the proximal common bile duct.

b) Fusiform dilatation of the common bile duct (CBD) with suspected intraductal sludge or calculi, consistent with a Todani Type IC choledochal cyst and associated choledocholithiasis

Patient was definitively treated via laparoscopic excision with Roux-en-Y hepaticojejunostomy by the pediatric surgery division. Intraoperative imaging **(Figure 2A–D)** provides a stepwise depiction of the surgical field. Reconstruction was performed with a Roux-en-Y hepaticojejunostomy and a side-to-side jejunojejunostomy, with tension-free anastomoses. A 14 Fr subhepatic drain was placed. Postoperatively, she remained hemodynamically stable in the PICU, without bile leakage or infectious complications. Enteral feeding resumed on postoperative day four. Histopathology confirmed a choledochal cyst without dysplasia or malignancy **(Figure 3)**. She was discharged on postoperative day seven and has remained asymptomatic with normal laboratory results on follow-up.

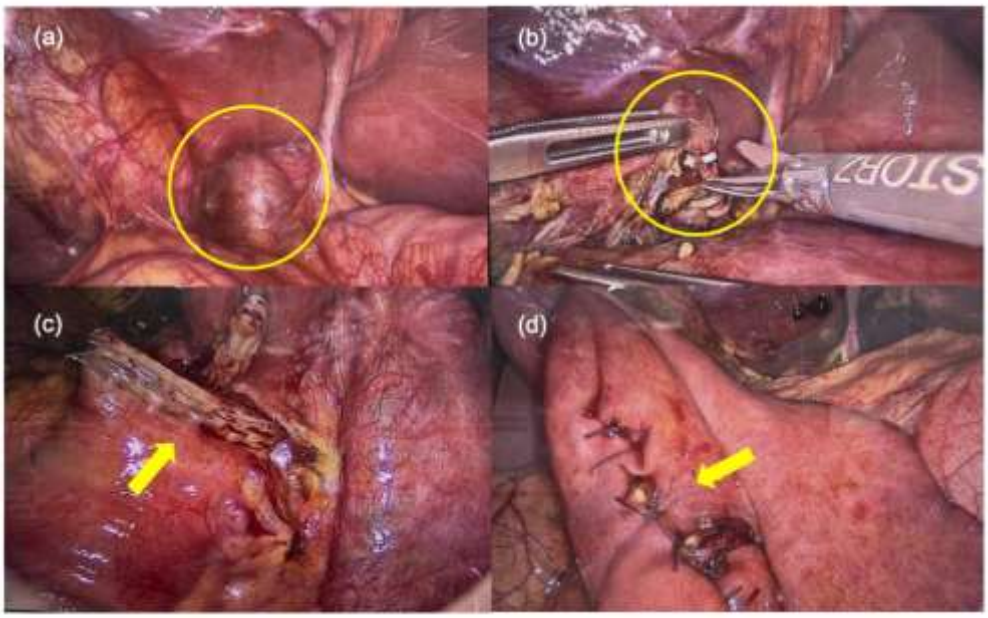

Figure 2. Laparascopic Roux-en-Y hepaticojejunostomy
a) Fusiform choledochal cyst
b) Ligated choledochal cyst
c) Hepatico-jejunostomy
d) Jejunum-jejunostomy

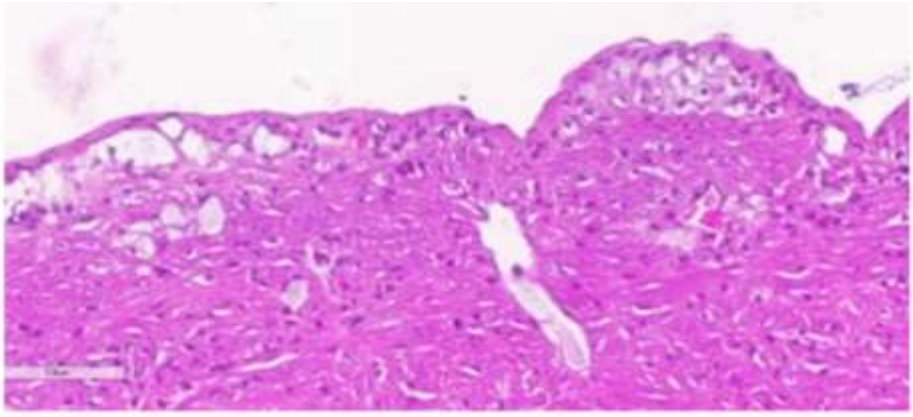

Figure 3. Histomorphology result showed columnar epithelium with no sign of malignancy

Discussion

Unlike most reported cases, this patient demonstrated overlapping clinical and radiologic features suggestive of autoimmune pancreatitis, leading to temporary immunosuppressive treatment before the definitive biliary etiology was identified.

The Role of Choledocal Cysts in Choledocholithiasis and Recurrent Pancreatitis

Choledocholithiasis is uncommon in children compared to adults.[5, 6] When clinical signs are present, they frequently resemble other gastrointestinal conditions. Diagnostic confirmation of gallstones and choledocholithiasis primarily depends on imaging, with transabdominal ultrasonography serving as the initial modality of choice. Nevertheless, ultrasound has limited sensitivity for detecting stones within the common bile duct, especially when ductal dilatation is absent. In such cases, advanced imaging techniques such as magnetic resonance cholangiopancreatography (MRCP) or contrast-enhanced computed tomography (CT) are often necessary to better define the biliary anatomy.[7]

The presence of gallstones or biliary sludge in the common bile duct may intermittently obstruct the pancreaticobiliary junction, leading to retrograde bile flow, premature activation of pancreatic enzymes, and subsequent pancreatic inflammation. In the pediatric population, recurrent inflammation without timely diagnosis and intervention may result in progressive pancreatic damage and chronic sequelae.[10, 11] Markers of biliary pancreatitis in children include significantly elevated liver transaminases (particularly ALT >150 U/L), hyperbilirubinemia, elevated gamma-glutamyl transferase (GGT), and pancreatic enzymes such as serum amylase and lipase.[5, 6] Poffenberger et al. also emphasized the importance of clinical findings such as right upper quadrant (RUQ) tenderness, biliary colic, and postprandial exacerbation of symptoms.[5]

Choledochal cysts (CCs) represent congenital malformations of the biliary tract, defined by cystic dilatation of the bile ducts. According to the Todani classification, type IC is marked by fusiform enlargement of the extrahepatic bile duct and is often linked to an anomalous pancreaticobiliary junction (APBJ). This anatomical variation allows pancreatic secretions to reflux into the biliary system, leading to chronic inflammation and injury of the biliary epithelium.[1, 2, 10, 11] Definitive diagnosis often requires advanced imaging, with MRCP and CT being especially useful for mapping the biliary anatomy and identifying complications.[10, 11]

Comprehensive assessment for choledochal cysts is crucial in pediatric patients presenting with choledocholithiasis, as these cysts represent a frequent underlying etiology in children. Failure to identify and treat an associated choledochal cyst can leave the disease unaddressed, predisposing to recurrent gallstone formation and

chronic pancreatitis. In the present case, a Type IC choledochal cyst (CC) was diagnosed based on imaging that demonstrated fusiform dilatation, suspected choledocholithiasis, and a history of recurrent pancreatitis. Surgical management involved cholecystectomy combined with laparoscopic Roux-en-Y hepaticojejunostomy to correct the biliary anomaly. Histopathological analysis revealed chronic inflammatory changes, consistent with long-standing biliary tract pathology.[1, 4]

Diagnostic Challenges and Possibility of Autoimmune Pancreatitis

Autoimmune pancreatitis (AIP) is a rare cause of chronic pancreatitis that can be difficult to diagnose in children due to its nonspecific symptoms and overlap with other pancreatic diseases. The initial consideration of autoimmune pancreatitis arose because the patient exhibited recurrent episodes of pancreatitis without a demonstrable structural etiology on early imaging, an indication in which AIP should be evaluated according to the International Consensus Diagnostic Criteria (ICDC), which synthesize parenchymal and ductal imaging, serology, other-organ involvement, histopathology, and response to steroids as the core diagnostic domains.[12] The MSCT demonstrated diffuse gland enlargement with a classic "sausage-shaped" pancreatic morphology, fulfilling an ICDC Level 1 parenchymal imaging criterion, thereby strengthening the preliminary suspicion of AIP.[13] Due to substantial diagnostic constraints in Bali, where IgG4 quantification, pancreas-specific autoantibodies, and OOI-related assays are not routinely available, the immunologic assessment was restricted to ANA immunofluorescence and ANA profile testing, representing an incomplete but pragmatic approach to fulfilling the serologic domain. This limitation significantly reduces diagnostic confidence and increases over-reliance on partial criteria and steroid trials.[12-14] Methotrexate was instituted as a steroid-sparing immunomodulator following an initial intravenous methylprednisolone course to permit outpatient continuation of immunosuppression and to limit cumulative glucocorticoid exposure.[14, 15] Methotrexate use in this patient (oral, weekly dosing as per institutional practice) therefore represented a pragmatic approach to maintain disease control in the outpatient setting. However, Methotrexate use in this case should not be interpreted as standard pediatric practice but rather as a context-driven decision in a resource-limited setting.

Nonetheless, AIP was ultimately excluded when the patient's symptoms recurred during and after steroid tapering, and her pancreatitis biomarkers did not exhibit the expected biochemical resolution, a pattern discordant with the rapid and consistent steroid-responsive trajectory documented in both adult and pediatric AIP cohorts.[16-18] These considerations prompted renewed etiologic investigation. MRI evaluation was performed in consultation with a pediatric radiology subspecialist subsequently revealed choledocholithiasis and a Todani type IC choledochal cyst, providing a

definitive structural cause for the patient's recurrent pancreatitis and replacing the earlier working diagnosis of AIP.

Timely Diagnosis and Surgical Intervention

The mainstay of treatment for choledochal cysts, particularly when complicated by choledocholithiasis and pancreatitis, is complete cyst excision and biliary-enteric reconstruction. Roux-en-Y hepaticojejunostomy is the preferred surgical technique due to its durability and reduced risk of complications such as bile reflux and cholangitis compared to hepaticoduodenostomy.[19, 20] The laparoscopic approach, although needed advance skill and experience, offers advantages such as reduced surgical trauma, faster recovery, and improved cosmesis and has become standard in specialized pediatric centers.[21]

In this patient, laparoscopic Roux-en-Y hepaticojejunostomy with complete cyst and gallbladder excision was performed. Consistent with pediatric recommendations, postoperative evaluation following choledochal cyst excision requires longitudinal monitoring to detect late complications such as anastomotic stricture, recurrent ductal dilatation, cholangitis, or hepatic fibrosis.[22] Current pediatric series and guidelines advocate structured follow-up comprising clinical evaluation and liver function tests at 1, 3, and 6 months postoperatively, supplemented by abdominal ultrasonography or MRCP during the first postoperative year and annually thereafter, or more frequently if symptoms or biochemical abnormalities emerge.[23, 24] In this patient, an early outpatient review on postoperative day 14 demonstrated complete clinical resolution and normalized laboratory parameters.

Conclusion

This case emphasizes the diagnostic challenges of pediatric biliary pancreatitis in children, particularly when autoimmune markers and imaging results yield borderline findings. Structural biliary disease should remain a diagnostic priority in pediatric recurrent pancreatitis, even in the presence of autoimmune-like features. Given the often nonspecific clinical manifestation, a multidisciplinary and comprehensive evaluation is essential through early collaboration among pediatric gastroenterology, radiology, surgery, and other relevant specialties to facilitate timely diagnosis and optimize clinical outcomes.

Acknowledgement

This case report has received consent for publication from the subject and parents.

Conflict of Interest

This case report has no conflict of interest

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APGHN Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Case Report

Symptomatic Cholelithiasis in a Male Infant: Two-Year Follow-Up and Surgical Management – A Case Report

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Abstract:

Background: Infant cholelithiasis is an uncommon and often idiopathic condition, frequently detected incidentally due to nonspecific symptoms. Although spontaneous resolution is common during infancy, the lack of standardized management guidelines complicates decision-making, particularly in symptomatic patients. Long-term data describing the natural history and indications for surgical intervention remain limited.

***Case*:** We describe a male infant diagnosed with gallstones at four months of age following recurrent episodes of colicky abdominal pain. Extensive laboratory evaluation excluded hemolytic, metabolic, infectious, and anatomical causes. Serial ultrasonography confirmed persistent gallstones without inflammatory changes. Given the patient's clinical stability, expectant management with close follow-up was initially chosen, including periodic clinical assessments, annual ultrasound examinations, and biochemical testing. Despite normal growth and normal biochemical results, the patient experienced intermittent recurrent localized abdominal pain over a two-year period. Because of persistent symptoms, definitive surgical management was indicated, and an open cholecystectomy was performed at two years of age. Intraoperative findings revealed two black pigment stones consisting of calcium bilirubinate, without anatomical abnormalities. Postoperative recovery was uneventful, and the patient remained asymptomatic during follow-up.

***Discussion*:** This case illustrates the challenges of managing idiopathic infant cholelithiasis, particularly regarding the timing of surgery. While conservative management is appropriate for asymptomatic patients, persistent or recurrent symptoms justify surgical intervention. This extended follow-up provides insight into the persistence of the disease beyond infancy.

Conclusion: Individualized management is essential in infant cholelithiasis. This case supports surgical treatment in symptomatic patients with persistent gallstones, even in the absence of identifiable risk factors.

Keywords: cholecystectomy, cholelithiasis, gallstones, infant, pediatric cholelithiasis

Introduction

Gallstones are defined as solid deposits, including stones or biliary sludge, within the gallbladder (cholelithiasis) or biliary tract, arising from altered bile composition, gallbladder motility, and genetic or metabolic factors.[1, 2] In adults, prevalence is up to 16%, especially in older adults.[3] The widespread use of ultrasonography has enabled earlier and more accurate diagnosis, often detected incidentally.[4] In pediatric populations, prevalence is less than or equal to 2%, with 33–40% of cases being asymptomatic.[2, 5] Distribution varies by age and sex; more frequent in girls older than 10 years and in boys younger than 2 years. In infants, cholelithiasis is rare and often idiopathic, though it may be linked to hereditary, metabolic, or infectious factors, prolonged parenteral nutrition, or medication use.[2] Diagnosis is challenging, since symptoms are nonspecific and may overlap with other abdominal disorders.[6] We report a case of idiopathic cholelithiasis diagnosed at 4 months of age, initially managed expectantly. The patient ultimately required cholecystectomy at 2 years, underscoring its low incidence, diagnostic challenges, and the need for standardized management protocols.

Case

A two-year-old boy, delivered at term following a fifth uneventful pregnancy with appropriate prenatal care, did not require resuscitation and was discharged without perinatal complications. He was exclusively breastfed, received all recommended vaccinations, and had a normal newborn screening test. The child lives in adequate sanitary conditions, and his parents were healthy, with no relevant family history of hemolytic, metabolic, or hepatobiliary disease. Subsequent follow-up confirmed normal growth and neurological development.

At four months of age, the patient presented with recurrent episodes of paroxysmal abdominal pain, characterized by sudden-onset, high-pitched, inconsolable crying associated with irritability, body flexion, and crying triggered predominantly after feeding, partially relieved by spontaneous calming, and clearly distinct from typical infantile colic. There were no associated symptoms such as fever, vomiting, diarrhea, jaundice, acholic stools, or failure to thrive.

Due to recurrent abdominal pain, the patient was taken by his parents to a private clinic, where an ultrasound revealed gallstones. However, no written report was provided at that time, and the patient was subsequently referred for pediatric surgical evaluation without documentation. On examination, the child was afebrile and hemodynamically stable, with intermittent irritability and suspected right upper quadrant discomfort, without abdominal distension or palpable masses.

Initial laboratory evaluation included complete blood count, serum biochemistry, electrolytes, lipid profile, coagulation test, pancreatic enzymes, hemolysis panel (reticulocyte count, lactate dehydrogenase, haptoglobin, and peripheral smear), inflammatory markers, and urinalysis, all which were within normal limits. As shown in **Table 1**, liver function tests demonstrated a transient cholestatic pattern, with elevated alkaline phosphatase and gamma-glutamyl transferase and mild transaminase elevation, without progressive hyperbilirubinemia. These findings effectively ruled out hemolytic, infectious, and metabolic causes of cholelithiasis.

Table 1. Initial liver function tests with appropriate values for a 4-month-old infant

Biochemical variable	Normal for age	Result
Total bilirubin (mg/dl)	0.05-0.68	0.78*
Indirect bilirubin (mg/dl)	0-1	0.32
Direct bilirubin (mg/dl)	0.05-0.30	0.46*
Alkaline phosphatase (U/L)	134-518	655*
Albumin (g/dl)	2.8-4.7	4.09
Total protein (g/dl)	4.2-7.4	6.2
Alanine transaminase (ALT) (U/L)	5-33	49*
Aspartate transaminase (AST) (U/L)	20-67	74*
Gamma-glutamyl transpeptidase (GGT) (U/L)	5-65	82*

* = Outside the reference range

Other frequent causes of abdominal pain in infancy, including cow's milk protein allergy and functional gastrointestinal disorders, were excluded based on exclusive breastfeeding, absence of alarm signs (poor weight gain, persistent vomiting, gastrointestinal bleeding), normal physical examination, and appropriate developmental progression. Institutional ultrasound **(Figure 1A and 1B)** demonstrated a heterogeneous gallbladder with a 1.3 mm wall and two hyperechoic oval images located in the gallbladder neck, measuring 13 and 7 mm, respectively, with posterior acoustic shadowing. No biliary duct dilatation, choledochal cyst, or structural abnormalities were identified, and there were no sonographic signs of cholecystitis.

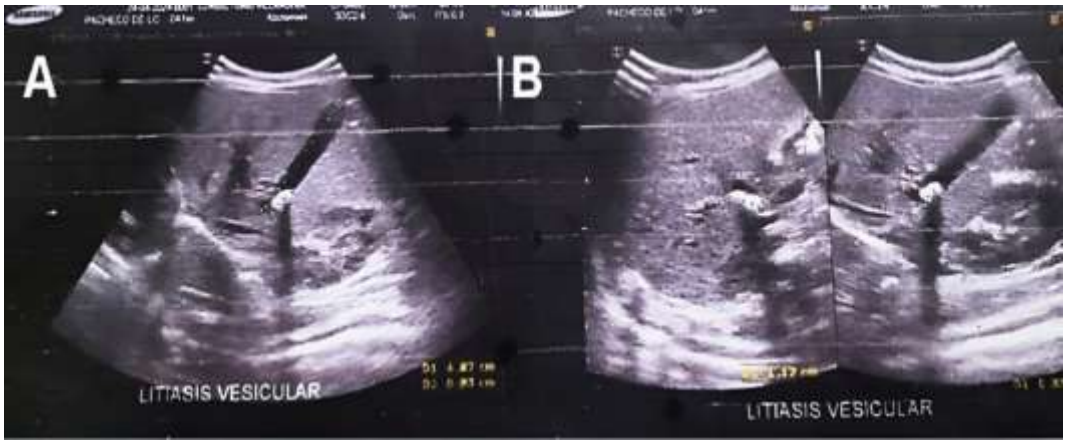

Figure 1. Ultrasonographic findings of the gallbladder.

a) Longitudinal ultrasound view demonstrating a distended gallbladder with a thin, regular wall and preserved mural stratification. Within the gallbladder neck, a well-defined echogenic focus with strong posterior acoustic shadowing is identified, consistent with a solid gallstone. No pericholecystic fluid or gallbladder wall thickening is observed, findings that argue against acute cholecystitis.

b) Additional views in longitudinal and oblique orientations reveal two discrete echogenic foci, both casting clean, sharp acoustic shadows, located within the gallbladder lumen. Their non-mobile appearance (given the similar position across sequential frames) suggests they are impacted or partially impacted pigment stones. The surrounding biliary tree shows no evidence of ductal dilatation.

Given the patient's clinical stability, young age, absence of complications, and socioeconomic limitations affecting access to specialized care, expectant management was initially selected. This approach was based on pediatric guidelines supporting conservative management in asymptomatic or mildly symptomatic infants. Follow-up consisted of scheduled clinical evaluations every 6 months, parental symptom diaries, growth and nutritional monitoring, serial abdominal ultrasonography annually, and biochemical testing including liver function tests, bilirubin levels and complete blood count. Laboratory parameters were consistently normal during follow-up, supporting an idiopathic etiology, while serial ultrasounds demonstrated persistent gallstones without change in size or number. Also, the patient remained clinically asymptomatic throughout the first year, with no recurrence of abdominal pain and normal growth. During the second year of follow-up, however, he developed two consecutive episodes of localized colicky abdominal pain within a one-week period, which prompted medical consultations. These episodes were managed conservatively with intermittent oral analgesics (acetaminophen), with adequate symptomatic relief. Due to persistent, recurrent colicky pain over a two-year period, definitive surgical management was indicated in accordance with pediatric surgical recommendations, and an open cholecystectomy was performed at two years of age after completion of the preoperative evaluation.

On admission, the patient was asymptomatic, afebrile, and hemodynamically stable, weighing 12.2 kg and measuring 85 cm. Physical examination revealed intact neurological status, appropriate social interaction, clear lung fields, a regular heart rhythm without murmurs, and a soft, non-tender abdomen with normal bowel sounds and no organomegaly. The patient underwent open cholecystectomy via a right subcostal Kocher incision. Intraoperative findings included a gallbladder measuring approximately 5 × 2 cm with minor adhesions at the neck (Parkland grade II). Two gallstones were identified: one in the gallbladder body and another in Hartmann's pouch. Both were hard, irregular, and black, consistent with pigment stones, the most common type in pediatric patients, associated with calcium bilirubinate precipitation. These findings are shown in **Figure 2A and 2B** depicting the gallbladder and extracted stones. No acute inflammation or anatomical anomalies were observed.

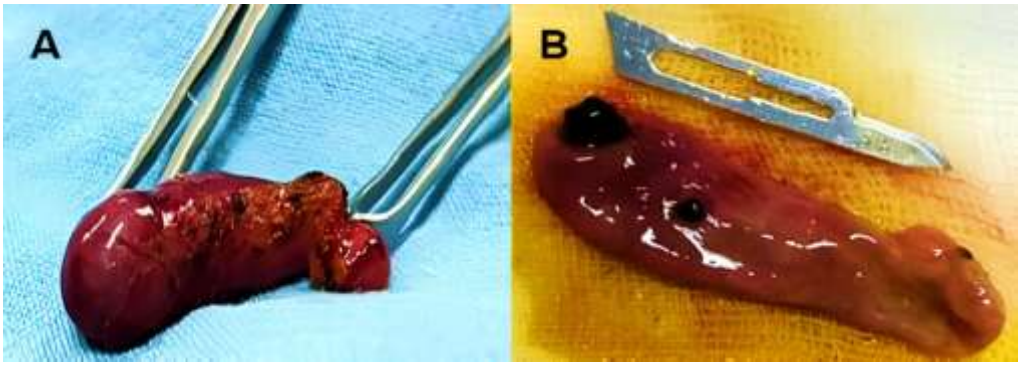

Figure 2. Macroscopic appearance of the gallbladder and pigment stones.

a) Intact gallbladder with thin walls and a smooth, glistening serosal surface, without features of acute inflammation. Mild focal congestion is noted near the neck, correlating with the minor adhesions described intraoperatively. No mural thickening, perforation, or anatomical anomalies are observed.

b) Gallbladder opened longitudinally, revealing a preserved and uniformly smooth mucosal surface without ulceration or erosions. Two black pigment stones with irregular contours and firm consistency are identified within the lumen, located in the body and infundibulum. Their dark coloration and density are consistent with calcium bilirubinate pigment stones, the most common type in pediatric patients.

Histopathological examination revealed a gallbladder with congested mucosa and nonspecific chronic changes, without dysplasia or malignancy. Two black pigment stones composed predominantly of calcium bilirubinate, with no significant cholesterol component, were confirmed. The postoperative course was uneventful. The patient was discharged 36 hours later in good condition. Outpatient follow-up demonstrated favorable clinical progress, appropriate weight gain, and no recurrence of abdominal symptoms. Parents were advised to attend scheduled pediatric follow-

up visits and seek emergency care if alarming signs developed. Written informed consent was obtained from one of the parents for the publication of this case report.

Discussion

Cholelithiasis in childhood, particularly in infants under one year of age, is a rare but increasingly recognized clinical phenomenon due to the widespread use of abdominal ultrasonography.[4] Its etiology differs markedly from that observed in adults, with a predominance of secondary causes and a smaller, though still significant, proportion of idiopathic cases. The literature indicates that between 30% and 50% of gallstones diagnosed in the first months of life lack an identifiable causal factor, which underscores the need for rigorous diagnostic evaluation to classify a case as idiopathic.[1]

The etiological analysis is based on ruling out chronic hemolysis, liver disease, anatomical abnormalities, systemic infections, parenteral nutrition, and exposure to lithogenic drugs such as ceftriaxone, furosemide, or somatostatin analogs.[2] Although black pigment gallstones are classically associated with hemolytic diseases or conditions that cause hyperbilirubinemia, several pediatric series report that a significant proportion of infants and children with pigment stones lack identifiable risk factors, suggesting an idiopathic form. These stones remain predominantly pigment (calcium bilirubinate) and could form through biliary supersaturation with unconjugated bilirubin and precipitation of calcium salts.[7]

Ultrasound evidence plays a central role in the identification of cholelithiasis and its complications. Ultrasound has high sensitivity and specificity for detecting stones in childhood, making it the technique of choice due to its availability and safety.[4] In infants, its differential diagnostic value is especially relevant because the symptoms are often nonspecific and difficult to interpret.[1] Ultrasound confirmation by demonstrating mobile hyperechoic foci with posterior acoustic shadowing and excluding significant wall thickening, pericholecystic fluid, or dilation of the common bile duct allows differentiation between uncomplicated stones and inflammatory processes such as acute cholecystitis or choledocholithiasis.[8]

The literature agrees that most infants diagnosed with gallstones experience spontaneous resolution, especially when the stones are small or constitute biliary sludge.[5] It has been documented that between one-third and one-half of patients under 12 months of age experience complete resolution within an average of nine months, associated with physiological liver maturation. This trend supports the recommendation of expectant management in asymptomatic cases, along with serial ultrasounds every 3 to 6 months.[9] Furthermore, the use of ursodeoxycholic acid remains controversial: the most recent studies show higher resolution rates in untreated patients, suggesting that the improvement reflects the natural history rather

than a true pharmacological effect. Moreover, its efficacy is limited in pigment stones, which are predominant in the pediatric population.[10]

However, guidelines agree that the presence of persistent symptoms, especially recurrent colicky pain, is a formal indication for cholecystectomy, regardless of age.[1, 4] Evidence indicates that symptomatic infants have a higher risk of complications such as cholecystitis, pancreatitis, or stone migration, even without initial signs of inflammation.[8] Regarding the surgical approach, laparoscopic cholecystectomy is the standard in most centers due to its postoperative advantages.[1, 9] Nevertheless, in young infants, open surgery remains a completely valid and safe alternative.[1] Several pediatric reports show that there are no significant differences in complications between the two methods in children under one year of age, provided the technique is adapted to the anatomical context and the surgeon's experience.[1, 9]

This case adds value to the literature by exemplifying an idiopathic presentation of pigment stones in an infant without predisposing factors, whose persistent symptoms warranted intervention. It also underscores the importance of strictly applying diagnostic exclusion criteria, appropriately using ultrasonography as the primary diagnostic tool, and recognizing that, although spontaneous resolution is common, persistent symptoms necessitate definitive management.[1, 4, 5] The experience accumulated in these cases contributes to the understanding of the pathophysiology of lithiasis in infants and strengthens the evidence supporting surgical indications at an early age.

Conclusion

Cholelithiasis in infants is rare and often resolves spontaneously, but some cases persist and require intervention. This report highlights idiopathic pigment stones occurring without hemolysis or identifiable risk factors, supporting their recognition as a distinct entity. Persistent symptoms and stable or enlarging stones on serial ultrasounds justify definitive surgical management, regardless of age. Limited access to specialized care can prolong symptom burden, underscoring the need for tailored follow-up protocols in resource-constrained settings. Further research is necessary to elucidate the mechanisms of idiopathic pigment stones in early life and to establish standardized criteria for follow-up and surgical indication

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Informed written consent was obtained from one of the parents.

Conflict of Interest

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Literature Review

Chronotype and Chrononutrition Profiles in Adolescents Obesity

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Abstract:

Background: Adolescent obesity remains a major global public health challenge. Modern lifestyle factors that disrupt circadian rhythms may exacerbate metabolic dysregulation in adolescents. Chronotype, reflecting innate circadian preferences for sleep-wake and activity timing, and chrononutrition, which emphasizes the alignment of meal timing with circadian rhythms, have gained attention as potential determinants of obesity. However, evidence integrating chronotype and chrononutrition profiles with adolescent obesity remains limited. Therefore, this review aims to synthesize the current evidence on the roles of chronotype and chrononutrition in adolescents obesity.

Discussion: Circadian rhythm regulates metabolic, hormonal, and behavioral processes through coordinated central and peripheral clocks. Variations in chronotype and disruptions in circadian alignment influence sleep patterns, meal timing, and metabolic regulation in adolescents. Evidence indicates that chronotype alone does not directly determine obesity risk; rather, its interaction with eating timing, sleep quality, and lifestyle behaviors plays a crucial role. Chrononutrition emphasizes aligning food intake with the biologically active phase, which is associated with improved insulin sensitivity, glycemic control, lipid metabolism, and blood pressure regulation. Determining chronotype and chrononutrition profiles remains challenging. The assessment is predominantly performed using standardized and validated questionnaires.

Conclusion: Chronotype and chrononutrition profiles may contribute to the risk of obesity in adolescents. They might be a potential strategy for obesity prevention and management. Nevertheless, current evidence remains limited, and further longitudinal and interventional studies are required to confirm these findings and inform future recommendations.

Keywords: chrononutrition, chronotype, obesity, adolescents, profiles

Introduction

Adolescent obesity remains a major global health challenge, with a prevalence of approximately 5% according to the Global Burden of Disease Obesity Collaborators.[1] Data from the World Health Organization indicate that more than 390 million children and adolescents aged 5 – 19 years were overweight, with prevalence increasing markedly from 8% in 1990 to 20% in 2022. The prevalence of obesity among children and adolescents also increased substantially, from 2% (approximately 31 million children) in 1990 to 8% (approximately 160 million children and adolescents) in 2022.[2] This condition not only increases the risk of non-communicable diseases in adulthood, such as type 2 diabetes mellitus, hypertension, and cardiovascular disease, but also adversely affects psychosocial well-being, cognitive development, and overall quality of life among adolescents.[3, 4]

Multiple risk factors for adolescent obesity have been identified, including high-calorie and low-fiber dietary patterns, insufficient physical activity, sedentary behavior, poor sleep quality, genetic predisposition, and the family environment. A study by Mahumud et al. demonstrated that consumption of sugar-sweetened beverages, fast food, low physical activity, and sedentary behaviors such as excessive screen time were significantly associated with obesity.[5]

Beyond these established factors, individual variation in daily biological rhythms, or chronotype, may also influence obesity risk. Chronotype refers to an individual's innate preference for sleeping and engaging in activities at specific times within a 24-hour cycle, reflecting underlying circadian rhythm characteristics.[6] These rhythms are regulated by the suprachiasmatic nucleus (SCN) in the brain and are synchronized with the environment through zeitgebers (external cues), such as light exposure, dietary patterns, and physical activity.[7]

Modern lifestyle changes, such as exposure to artificial light at night, irregular sleep patterns including late-night activities, and working during biological rest periods, disrupt the body's circadian rhythm and lead to chronodisruption or circadian desynchronization.[4] Misalignment between an individual's chronotype and socially imposed schedules, known as social jetlag, may trigger hormonal dysregulation, alterations in eating behavior, and reduced physical activity, all of which contribute to increased fat accumulation.[6, 8]

Traditional nutritional approaches have primarily focused on dietary composition and caloric intake, with limited consideration of biological timing and individual chronotype. In this context, chronotype and chrononutrition have emerged as novel approaches that integrate circadian biology into nutritional strategies. Chrononutrition is an approach aimed at realigning circadian rhythm desynchronization by evaluating

individual eating patterns and behaviors to prevent disease risk and predict potential increases in such risk.[9]

Based on circadian rhythms, the light phase in the morning represents an optimal window for food intake, during which nutrient consumption can help optimize circadian function by coordinating peripheral and central circadian rhythms. Chrononutrition is expected to provide an effective nutritional strategy by optimizing meal timing in alignment with circadian rhythms, thereby helping prevent and reduce the risk of various diseases.[9, 10] Despite growing evidence, a comprehensive synthesis of chronotype and chrononutrition profiles as temporal determinants of obesity in adolescents remains limited. Therefore, this literature review addresses this gap.

Circadian Rhythm

The circadian rhythm is a central pacemaker system that regulates most biological processes by coordinating molecular, physiological, hormonal, and behavioral rhythms in alignment with the 24-hour light–dark cycle. This endogenous system maintains internal homeostasis and enables optimal metabolic responses to environmental changes.[11, 12]

The central circadian clock is located in the SCN of the anterior hypothalamus, which functions as the master pacemaker. The SCN operates in coordination with peripheral oscillators distributed across nearly all tissues and cells. It receives photic input from the retina and synchronizes peripheral clocks through neural and hormonal signaling pathways. Although each cell contains an intrinsic molecular clock, synchronization by the SCN ensures that physiological rhythms remain aligned with the 24-hour light–dark cycle, allowing optimal temporal coordination of biological processes.[13, 14]

Circadian rhythms are generated by a transcription–translation feedback loop involving positive and negative clock components. The positive elements, CLOCK (Circadian Locomotor Output Cycles Kaput) and BMAL1 (Brain and Muscle ARNT-Like 1), form a heterodimer that activates the transcription of negative regulators, including Period (PER1, PER2, PER3), Cryptochrome (CRY1, CRY2), and Rev-Erbα. The translated PER and CRY proteins accumulate in the cytoplasm, form PER–CRY complexes, and subsequently translocate into the nucleus to inhibit CLOCK–BMAL1 activity. This inhibition suppresses PER and CRY transcription until the inhibitory complexes are degraded via proteolytic pathways, thereby relieving repression and initiating the next circadian cycle, which recurs approximately every 24 hours.[13, 14]

Chronotype and Chronodisruption Definitions

The Chronotype refers to an individual's tendency to engage in daily activities according to their intrinsic circadian rhythm. It reflects a person's natural preference for sleep and wake times, influenced by the internal biological clock. These patterns

can affect levels of alertness, productivity, mood, and overall physical and mental health throughout the day. Chronotypes are generally classified into three categories:[11, 15]

a. Morning chronotype, characterized by a preference for earlier wake times and earlier sleep onset;
b. Evening chronotype, characterized by a preference for later sleep onset and waking at later hours; and
c. Intermediate chronotype refers to individuals who do not distinctly align with either the morning or evening type, exhibiting sleep-wake patterns that fall between the two extremes.

Morning chronotypes are commonly referred to as "early birds, whereas evening chronotypes are known as "night owls.".[16] Individuals with a morning chronotype generally exhibit an advanced sleep phase (ASP), earlier wake times, higher levels of alertness, and optimal performance during the morning hours, and a circadian rhythm period that tends to be shorter than 24.2 hours. In contrast, individuals with an evening chronotype are characterized by a delayed sleep phase (DSP), later wake times, a preference for activities during the afternoon to evening hours, and a circadian rhythm period that tends to be longer than 24.2 hours.[11, 16] Individuals who fall between these two chronotypes are classified as having an intermediate chronotype.[17] Individual differences in chronotype are influenced by internal factors such as age, sex, and genetic background.[16, 18] These genetic variations are known to contribute to differences in sleep patterns, caloric intake, waist circumference, obesity, and the presence of other metabolic disorders.[19]

Chronodisruption describes a condition in which the body's circadian rhythm is disrupted or misaligned. This term encompasses various forms of circadian desynchronization that may affect physiological, hormonal, metabolic, and behavioral functions.[9] Some experts distinguish between terms used to describe this desynchronization. For instance, chronodisturbance refers to circadian misalignment that still allows physiological adaptation without significant adverse health effects. In contrast, chronodisruption is more specifically applied when such desynchronization increases the risk of health disorders or disease.[20]

Chrononutrition

The chrononutrition is a dietary approach that adjusts food intake to an individual's biological clock. This concept emphasizes the importance of determining the optimal time to eat by taking into account the body's physiological readiness to digest and metabolize nutrients. Therefore, attention to food quality and quantity needs to be followed by choosing the right time to eat. In addition, chrononutrition emphasizes the importance of consistency in meal schedules and frequency, as well as the incorporation of nutrient-dense foods into daily consumption patterns.[9]

Diet interventions that synchronize food consumption with individual circadian rhythms, such as time-restricted feeding (TRF), can benefit metabolic health. Research shows that TRF can improve glucose tolerance, reduce insulin resistance, and improve various cardiometabolic parameters, even without strict calorie restriction. These effects are closely related to the role of meal timing as a *zeitgeber*, which is an external time cue that regulates the expression of circadian genes in peripheral tissues such as the liver, muscles, and adipose tissue.[12]

Application of chrononutrition in clinical practice still faces various challenges. Many findings come from animal models, particularly mice, which are nocturnal, whereas humans are diurnal. This limits the relevance of preclinical results. Additionally, human studies are limited by lifestyle variability, adherence to dietary protocols, and heterogeneity in individual chronotypes, which influence physiological responses to time-restricted eating interventions. Chrononutrition has great potential for holistically improving metabolic health. The integration of nutrition science and molecular biology will be key to developing effective, clinically relevant nutritional interventions to prevent and manage metabolic diseases.[21]

Chronotype and Obesity

The Research examining the association between chronotype and obesity in adolescents remains limited, and direct comparisons across studies are challenging due to variability in the variables assessed. First, the obesity indicators used across studies vary considerably. Most studies rely on body mass index (BMI) as the primary parameter. In contrast, only a few use more specific and sensitive indicators, such as waist circumference or waist-to-height ratio. Second, differences in the control of confounding variables may affect study results. Factors such as age, sex, socioeconomic status, sleep duration and quality, physical activity, sedentary behavior, screen time, dietary patterns, and total energy intake are associated with both chronotype and obesity. Some studies report significant associations between chronotype and obesity; however, these associations become non-significant after adjustment for the previously mentioned variable. Third, heterogeneity in chronotype assessment instruments and classification criteria further complicates comparisons across studies. Some studies classify participants into morning and evening types only, while others include an intermediate category or use alternative classifications such as early and late chronotypes. In addition, correlations between different chronotype questionnaires may decrease after adjustment for age, sex, and sleep debt.[22, 23]

In adolescents, an evening chronotype has been associated with higher body mass index, increased fast food consumption, and a greater tendency toward pathological eating behaviors, such as night eating syndrome and food addiction.[24] However, the Eating Healthy and Daily Life Activities (EHDLA) Study demonstrated that adolescents with a morning chronotype had a 1.67-fold higher risk of central obesity

compared with those with an intermediate chronotype, as assessed using the waist-to-height ratio.[24, 25] In contrast to many previous studies, the EHDLA Study did not find a significant association between evening chronotype and obesity in adolescents. These findings suggest that chronotype alone is not a stand-alone determinant of obesity risk.[25]

Besides chronotype, other biological factors also play an important role, particularly sleep and eating habits. An evening chronotype is often associated with shorter sleep duration and poorer sleep quality due to misalignment between the biological clock and social demands, such as school or work schedules. However, other studies have reported that poor sleep quality can also be observed in individuals with a morning chronotype and is associated with increased adiposity indicators.[26]

From a dietary perspective, even when total energy intake does not differ substantially, chronotype influences the daily timing and distribution of food intake. Individuals with a morning chronotype tend to consume a greater proportion of their energy at breakfast, whereas those with an evening chronotype consume more energy during the evening.[25]

Puberty and Obesity

Puberty is a developmental process during which reproductive capacity is attained and is characterized by rapid somatic growth and substantial endocrine maturation.[27] One of the key hormones involved is growth hormone (GH). During the pubertal transition, GH secretion increases in a pulsatile manner to support the growth spurt and tissue remodeling. Adequate and well-regulated GH activity is essential for normal linear growth, changes in body composition, and metabolic homeostasis.[28] GH secretion during adolescence is closely linked to slow-wave sleep and circadian regulation; hence, its disruption of sleep timing or circadian alignment during this critical period may interfere not only with growth processes but also with metabolic regulation.[29] Consequently, puberty may increase susceptibility to metabolic dysregulation when combined with other risk factors, such as insufficient sleep, late-night eating, and reduced physical activity.[5]

Chrononutrition and Obesity

The chrononutrition emphasizes the importance of aligning eating schedules with circadian rhythms to maintain metabolic health. It highlights not only *what* to eat, but also *when* to eat. Several studies have demonstrated that meal timing functions not only as a source of energy but also as a regulator of biological rhythms.[30]

Several nutritional components influence the biological clock, both at the central level in the SCN and at peripheral clocks in body tissues. High-fat diets have been reported to act as triggers for chronodisruption, adversely affecting multiple metabolic

parameters. In contrast, ketogenic diets, which rely primarily on fat as the main energy source, have been shown to activate several clock-controlled genes (CCGs) through the CLOCK–BMAL1 signaling pathway.[30] High salt intake has also been reported to delay BMAL1 activation and suppress the expression of PER2 and CRY1. In addition, caffeine and theophylline have been shown to lengthen circadian rhythms at the cellular level.[31]

Studies have shown that eating during the morning-to-afternoon period, which corresponds to the active phase of the circadian rhythm, is associated with optimal insulin sensitivity, better glycemic control, and a healthier lipid profile. Physiologically, genes and proteins that are more active in the afternoon are involved in energy metabolism, such as glycogenesis and lipogenesis. In contrast, late-night eating or food intake outside the active circadian phase is associated with increased visceral fat deposition, impaired glucose tolerance, and disruption of energy homeostasis.[32]

Based on circadian rhythm principles, it is recommended to emphasize the distribution of calories and carbohydrates during the morning-to-afternoon period and to restrict the daily eating window to less than 10 hours from the first to the last meal. Time-restricted eating limited to the morning and afternoon has been shown to promote weight loss and improve metabolic parameters without requiring changes in total daily caloric intake.[24, 33]

Regular meal patterns, such as three main meals per day with healthy snacks in between, are also recommended to maintain harmony in biological rhythms. Misalignment with these eating patterns, together with irregular sleep schedules, may increase total energy intake, disrupt circadian rhythms, and subsequently elevate the risk of metabolic dysfunction.[24, 33]

Chronotype also plays an important role, as adolescents tend to shift toward an evening chronotype, which is often associated with greater nighttime energy consumption, skipping breakfast, and a preference for high-glucose and high-fat foods. These behaviors may lead to social jetlag, which has been shown to correlate with a higher risk of obesity and metabolic syndrome in young populations.[24, 33]

Interventions that take chronotype into account, such as adjusting school schedules, aligning meal timing with the biological clock, and restricting evening screen time, may reduce the risk of obesity and improve metabolic health in adolescents.[32, 33] Integrating these strategies into public health policies could represent an effective preventive approach to address the rising prevalence of obesity among adolescents.

Chrononutrition and Metabolic Syndrome

Metabolic syndrome is defined as a condition arising from multiple cardiometabolic risk factors, including central obesity, insulin resistance, hypertension, and dyslipidemia. Late, irregular, or predominantly nighttime eating patterns may lead to circadian misalignment, which disrupts metabolic homeostasis. Circadian misalignment impairs metabolic regulation, leading to altered glucose control, elevated insulin levels, increased insulin resistance, and glucose responses resembling those of a prediabetic state.[34]

Insulin sensitivity, the body's capacity for glucose and lipid metabolism, and incretin secretion peak from the morning until the afternoon. Therefore, energy intake during this period is more efficiently utilized for metabolism rather than stored as triglycerides. In addition, morning food intake helps maintain energy homeostasis, suppresses ghrelin secretion, and reduces the risk of evening overeating. Conversely, evening food intake, when metabolic activity declines, is associated with increased insulin resistance, higher postprandial hyperglycemia, and enhanced hepatic lipogenesis.[34] Late-night eating also alters appetite-regulating hormones by reducing 24-hour serum leptin levels and increasing the 24-hour ghrelin– leptin ratio, thereby promoting hunger.[35]

Eating timing also affects blood pressure by modulating the autonomic nervous system. Food intake increases sympathetic activity regardless of timing; late-night eating induces sympathetic activation during a period that is physiologically dominated by parasympathetic tone, resulting in circadian misalignment. This misalignment further suppresses melatonin secretion, a hormone known to contribute to the blood pressure-lowering effect.[36]

Chronotype and Chrononutrition Profile Assessment

Determining chronotype and chrononutrition profiles remains challenging. However, identifying an individual's chronotype provides important clinical benefits, including the diagnosis and management of circadian sleep disorders, the prediction of adaptability to work schedules, and the optimization of performance by aligning sleep timing with circadian rhythms.[37] Similarly, assessment of chrononutrition profiles enables the alignment of meal timing with the circadian system, which may support targeted interventions for metabolic diseases in the future. Currently, most studies determine chronotype and chrononutrition using validated questionnaires.[38]

Chronotype

One of the most widely used tools for assessing chronotype is the Morningness–Eveningness Questionnaire (MEQ). This instrument comprises 19 items designed to assess an individual's morning or evening chronotype, based on personal preferences for sleep timing, wake-up time, and daily activities. The MEQ has been validated

across diverse populations, translated into multiple languages, and revised into alternative versions, including Smith's Composite Scale of Morningness (CSM) and the reduced Morningness–Eveningness Questionnaire (rMEQ) developed by Adan and Almirall.[37]

The Munich Chronotype Questionnaire (MCTQ) is more objective because it collects data on sleep patterns on weekdays and free days to calculate the midpoint of sleep and identify social jetlag. This instrument consists of questions about sleep time, wake-up time, sleep duration, and the duration it takes to fall asleep (sleep latency). The Mid-Sleep on Free Days (MSF) value is calculated as the midpoint between sleep and wake times on free days. To reduce bias arising from compensation for sleep debt on workdays, a correction value called MSFsc is used. The smaller the MSFsc, the more inclined a person is to be a morning type, while a large MSFsc indicates an evening type tendency.[8] The MCTQ has also undergone various validations with diverse sample characteristics, been translated into multiple languages, and modified into other forms such as MCTQshift for shift workers and μMCTQ for a short version.[37]

The Children's Chronotype Questionnaire (CCTQ) was adapted from MCTQ. It differs in that it includes parental reports on sleep and wake times, sleep latency, and sleep midpoint for children on regular schedules and on days without a specific schedule. The assessment reflects direct observation of the child's sleep patterns, wake-up habits, and preferred activity times. One advantage of CCTQ is that evaluations can be conducted on both school days and off days.[37] **Table 1** summarizes the differences between the questionnaires.

Chrononutrition

The CP-Q is one of the most widely used questionnaires for assessing chrononutrition profiles. It consists of two main domains: (1) chrononutrition preferences (the times participants choose to wake up, sleep, or eat) and (2) chrononutrition behavior (the actual times participants perform these activities). The CP-Q assesses the first and last meal times of the day, lunch and dinner times, breakfast habits, sleep and wake times, and meal-time preferences. Although this instrument provides a more comprehensive assessment, its use is currently limited to the general population and has not been specifically validated for children or adolescents.[39]

In addition to the CP-Q, other instruments often used to assess chrononutrition include the Meal Pattern Questionnaire (MPQ). This instrument is simple and is used to collect data on meal frequency, food types, and meal times within 24 hours. Participants are asked to report their general daily eating patterns, specify meal times, and select the appropriate category (breakfast, main meal, snack, or beverage). The main limitation of the MPQ is that it does not distinguish between eating patterns on

work/school days and day-offs, so variations in eating behavior between days cannot be optimally captured.[40]

Additionally, there is the Eating Pattern Questionnaire (EPQ). Unlike the MPQ, the EPQ allows meal-time assessment that distinguishes between work/school days and day-offs. Respondents were asked to rate the frequency of their food or beverage consumption with the answer choices "always," "sometimes," or "never." However, the use of this abstract term is a major limitation, as interpretation can vary between respondents. As a result, the instrument's sensitivity to variations in dietary patterns over time is relatively low, although it still provides a rough overview of eating behavior.[38] The differences among the questionnaires are presented in **Table 2.**

Table 1. Comparison of the chronotype assessment instrument

Instrument	Target age (years)	Number of items	Main output	Reliability	Validity	Advantages	Disadvantages
MEQ, Horne, 1976[41]	≥ 16	19	Morningness–eveningness score (16–86); 5 classifications	Cronbach's α = 0,83; test retest r = 0,89	Correlates with core temperature and DLMO (r > 0,70)	Simple, widely used, shortened version available (rMEQ)	Better at assessing preference, less sensitive to actual sleep behavior
MCTQ, Roenneberg, 2012[8]	≥ 14	±15	MSFsc, social jetlag	ICC > 0,80; MSFsc correlation with actigraphy r = 0,73	Valid against actigraphy and DLMO	Measures actual sleep behavior, measures social jetlag	Requires more data (work days vs off days), recall bias
µMCTQ, Ghotbi, 2020[42]	≥ 14	6	MSFsc, social jetlag	Correlation to MCTQ r = 0,92	Valid against MCTQ	Quick (<2 minutes)	Limited detail (doesn't measure sleep duration per segment)
CCTQ, werner, 2009[37]	4–11	27 (3 subscales)	Morninness–eveninness score, factual sleep time, sleep inertia	ICC = 0,85; α > 0,80	Correlates with actigraphy r = 0,61	Specific for children, parent-friendly format, minimal missing data	Requires parent report, limited validity for cross-cultural use

MEQ = Morningness-Eveningness Questionnaire; DLMO = Dim Light Melatonin Onset; rMEQ= reduced Morningness-Eveningness Questionnaire; MCTQ = Munich Chronotype Questionnaire; MSFsc = Mid-Sleep on Free days corrected; ICC = Intraclass Correlation Coefficient; µMCTQ = Ultrashort Munich Chronotype Questionnaire; CCTQ = Children's Chronotype Questionnaire

Table 2. Comparison of the chrononutrition assessment instrument

Instrument	Measurement	Validity (study results)	Advantages	Disadvantages
CP-Q, Veronda, 2020[38]	18 items containing open-ended and multiple-choice questions to assess preferences and actual behavior (waking up/sleeping, first/last meal, lunch/dinner time, breakfast & dinner)	Strong convergent validity for the food intake log & PSQI: correlation r = 0.39–0.91; 65–80% of variables were within ≤ 60 minutes of the actual log.[39]	Captures detailed chrononutrition profiles and includes the sleep–wake relationship with meal times; strong validity with objective measures	Only validated in adult populations, and not specifically designed for children/adolescents. This questionnaire is relatively longer and more complex than other questionnaires.
MPQ, Forslun D, 2002[40]	Respondents reported their daily eating habits over a 24-hours. Categories: main meals, breakfast, snacks, and beverages.	Construct validity for the Eating Disorder Examination: Spearman rho = 0.74–0.87.[43]	Simple, easy to use, and captures daily meal distribution, distinguishing between workdays and holidays.	Suitable for general diets, but not specific to chrononutrition
EPQ, Guirette, 2019[44]	Using qualitative frequency terms ("always," "sometimes," "never") for food/beverage consumption	Relative validity compared to 24-hour food records: reported to be reasonably consistent, without detailed quantitative correlation values. [44]	Improved on MPQ by distinguishing between workdays and holidays.	Frequency measurement uses qualitative terms

CP-Q = Chrononutrition Profile Questionnaire; PSQI = Pittsburgh Sleep Quality Index. MPQ = Meal Pattern Questionnaire; EPQ = Eating Pattern Questionnaire;

Studies on children have been conducted in several countries using various instruments, albeit in limited numbers. Some researchers developed new

questionnaires for their own study. These studies still show varying results because many studies on chronotype and chrononutrition have different operational definitions **(Table 3).**

Table 3. Existing studies with assessment of chronotype and chrononutrition

Researcher/ Design/ Place	Description	Instrument Used	Results
Vilela, 2019/ Prospective cohort/ Portugal[45]	Assessed the effect of the amount, type of food, and eating period of children at the age of 4 years on their weight at the age of 7 years	3-day food diaries to assess the type and amount of food, and CEBQ to assess chrononutrition	High calorie intake during lunch and dinner at age 4 increases the risk of overweight and obesity at age 7
Yu, 2020/ Cross-sectional/ Hong-Kong[46]	Assessed the relation between chronotype and eating patterns in school-aged children aged 7-11 years	CCTQ to assess chronotype, and a researcher-developed questionnaire to assess eating behavior	Boys with a night chronotype tend to skip breakfast Girls with a night chronotype tend to eat fast food
Jankovic, 2024/ Cross-sectional/ Germany[47]	Assessed the relation between the 'highest calorie intake' time and an individual's chronotype with body composition in a population of adolescents aged 9-16 years.	MCTQ to assess chronotype, and 3-day food diaries to assess food type and quantity	Adolescents with a night chronotype and the highest nighttime calorie intake exhibit an increase in fat-free mass index (FFMI) over time.

CCTQ: Children's Chronotype Questionnaire, CEBQ: Child Eating Behaviour Questionnaire, FFMI: Fat-Free Mass Index, MCTQ: Munich Chronotype Questionnaire

Clinical Implication

The Knowledge of the influence of chronotype and chrononutrition profiles on obesity in adolescents has led to several important clinical implications: (1) biologically rhythm-based lifestyle interventions, (2) a reference framework for health promotion, (3) implementation within school activities, (4) enhanced parental involvement in shaping sleep and eating behaviors, and (5) the utilization of eHealth approaches.

1. Biologically Rhythm–Based Lifestyle Interventions
   Lifestyle interventions that account for biological timing have been shown to improve metabolic health in adolescents. A study by Janković et al. demonstrated

that a social jetlag of >1 hour over 1 year was associated with a 2.4% reduction in body fat percentage among adolescents aged 14–18 years.[47] Intervention programs that incorporate consistent sleep schedules, limited nighttime screen exposure, and regular breakfast consumption have been shown to reduce triglyceride levels by up to 15%. In addition to improving metabolic health, these modifications enhance sleep quality, which, in turn, positively affects cognitive function and appetite regulation.[48]

2. Reference Framework for Health Promotion
   An understanding of chronotype and chrononutrition has important implications for health promotion, particularly among adolescents. Research indicates that interventions targeting meal timing and sleep patterns tailored to chronotype variations can influence obesity status, metabolic syndrome, and sleep disorders.[11] For example, aligning meal schedules with circadian rhythms has been shown to reduce body mass index by 1.2–1.8 kg/m² over 12 weeks in adolescents with an evening chronotype. Therefore, health promotion strategies should incorporate education on optimal meal timing. Such approaches can be implemented through schools and community programs in an age-appropriate manner.[34]

3. Implementation Within School Activities
   The successful implementation of chronotype- and chrononutrition-based interventions requires multidisciplinary collaboration involving healthcare professionals, teachers, and parents. The school environment plays a strategic role in shaping healthy sleep and eating patterns among school-aged children, including adolescents. Schools can integrate circadian rhythm concepts into the curriculum as part of health education initiatives.[11]

   Research has shown that delaying school start times by 30–60 minutes can increase average sleep duration by up to 35 minutes per night and improve academic performance scores by 4–5%. In addition, providing nutritious breakfast options in school cafeterias may help better align eating patterns with adolescents' biological rhythms. The combination of education, environmental modification, and institutional policies constitutes a critical foundation for effective and sustainable interventions.[49]

4. Enhancing Parental Involvement in Shaping Sleep and Eating Behaviors
   Parental involvement is a key component in the formation of healthy sleep habits and dietary patterns in adolescents. Monitoring sleep schedules, limiting electronic device use before bedtime, and providing evening meals at consistent times have been shown to reduce the risk of obesity by up to 23% among adolescents with an evening chronotype. Parental roles become increasingly crucial during the

pubertal transition, a period during which biological changes naturally shift chronotype toward the evening type.[48]

5. Utilization of eHealth
   Utilization of eHealth approaches has emerged as a promising innovation in the implementation of chronotype- and chrononutrition-based health promotion strategies. A study by Benítez-Andrades reported that the use of digital applications to monitor meal timing, sleep, and physical activity resulted in an average reduction in body mass index (BMI) of 0.9 kg/m² over six months among overweight adolescents. Such technologies enable personalized interventions, reminder systems, and real-time progress tracking. Integration of eHealth tools with school-based programs and routine health consultations may further extend the reach of these interventions. However, long-term effectiveness remains dependent on sustained support from families and the surrounding environment to maintain behavioral changes.[50]

Research Gap

The A limitation of this review is the scarce availability of interventional studies specifically examining chronotype- and chrononutrition-based strategies for managing adolescent obesity. The existing literature in adolescent populations is largely observational, predominantly comprising cross-sectional and prospective cohort designs.[40, 43, 44] Randomized controlled trials are therefore needed to clarify causal relationships and to evaluate the effectiveness of circadian-aligned interventions.

Overall, current evidence supports the view that chronotype and chrononutrition profiles are important determinants of obesity prevention and management among adolescents. This literature review is expected to serve as a scientific foundation for the development of nutritional and lifestyle interventions aligned with the circadian rhythms of obese adolescents, thereby informing future prevention and management strategies.

However, to date, research examining the relationships between chronotype, chrononutrition, and obesity in adolescents still presents several limitations. Existing studies employ heterogeneous questionnaire-based instruments, complicating direct comparisons of findings. Moreover, the risk of bias remains relatively high due to heterogeneity in population characteristics, including age, sex, socioeconomic status, sleep duration and quality, physical activity levels, sedentary behavior, screen time, dietary patterns, and total energy intake, all of which have been reported to be associated with both chronotype and obesity.

Furthermore, each chronotype assessment instrument has inherent limitations. The heterogeneity of measurement tools and chronotype classification criteria further

complicates the interpretation of findings across studies. Some studies categorize participants solely as morning or evening types, whereas others include an intermediate category or use alternative classifications, such as early and late chronotypes. These methodological variations contribute to inconsistencies in reported results and limit the generalizability of the existing evidence.

Conclusion

Chronotype and chrononutrition are critical determinants in obesity and may be considered in its prevention and management. Integrating circadian-aligned nutritional and lifestyle interventions tailored to the chronotype of obese adolescents' strategy to optimize metabolic health and improve the effectiveness of obesity prevention and treatment in this population. Therefore, further longitudinal and interventional studies with large sample sizes and multicenter designs are required to confirm these findings and inform future recommendations.

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Conflict of Interest

None declared.

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