

CHALLENGES OF TIMELY DIAGNOSIS OF BILIARY SYSTEM DISORDERS IN CHILDREN WITH CEREBRAL PALSY

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Abstract

Cerebral palsy (CP) is one of the most common causes of persistent motor disability in children. Disorders of the biliary system — functional dyskinesias, chronic cholecystitis, and cholelithiasis — are recorded in this patient population with significantly higher frequency than in the general pediatric population, yet remain chronically underestimated and are diagnosed with substantial delay. The aim of this review is to systematize the clinical, neurogenic, and iatrogenic factors that complicate the timely detection of biliary pathology in children with CP, and to analyze existing diagnostic approaches and prospective biomarkers. The review addresses autonomic dysregulation of gallbladder motility, the role of polypharmacy, nutritional deficiency, intestinal dysbiosis, and disruption of the gut–liver–brain axis. The diagnostic potential of ultrasonography, laboratory and biochemical tests is discussed, along with the prospects for applying biomarkers FGF21, GDF15, and total bile acids. Timely diagnosis of biliary pathology in children with CP requires a multidisciplinary approach and the development of specialized screening protocols.

Keywords: cerebral palsy, biliary system, biliary dyskinesia, cholelithiasis, diagnosis, biomarkers, autonomic dysfunction, anticonvulsants, FGF21, GDF15.

INTRODUCTION

Cerebral palsy (CP) represents a group of chronic non-progressive developmental disorders of movement and posture caused by injury to the immature brain in the perinatal period. According to epidemiological data, the prevalence of CP is 2–3 cases per 1,000 live births, and in countries with high rates of prematurity — up to 5–8 cases. CP is not an isolated motor disorder but a multisystem condition in which involvement of internal organs frequently remains overshadowed by orthopedic and neurological problems.

Among somatic comorbidities in children with CP, pathology of the gastrointestinal tract in general and the biliary system in particular occupies a special place. Disorders of gallbladder motility, changes in bile composition, cholelithiasis, and inflammatory lesions of the biliary tract occur in this patient population at rates significantly exceeding those among healthy children. Nevertheless, the clinical diagnosis of these conditions is associated with a number of specific difficulties: atypical pain syndrome, inability to communicate verbally in a substantial proportion of patients, masking of abdominal symptoms by spastic reactions, and complexity in interpreting laboratory data against a background of polypharmacy.

Biliary system pathology that is not detected in a timely manner in children with CP leads to the formation of chronic inflammatory diseases, cholelithiasis, impairment of nutritional status, and deterioration in the quality of life of patients and

their families. In recent years, data have emerged on the relationship between enterohepatic circulation of bile acids and neuroinflammation and the state of the central nervous system through the gut–liver–brain axis, opening new pathogenetic perspectives in the study of this problem.

The aim of this review is to systematize current data on the factors hindering timely diagnosis of biliary system disorders in children with CP, to evaluate available diagnostic tools, and to identify promising directions for clinical research.

1. BILIARY SYSTEM PATHOLOGY IN CP: PREVALENCE AND PATHOGENESIS

1.1. Epidemiological Data

According to a number of studies, the frequency of functional disorders of the biliary tract in children with CP reaches 30–60%, depending on the form and severity of the disease. The most vulnerable patients are those with severe CP (GMFCS IV–V), in whom pronounced immobilization, severe nutritional disorders, and maximum pharmacological burden coexist. Among structural changes, the most frequently identified are: deformation and dysfunction of the gallbladder, chronic gallbladder hypotonia with impaired bile evacuation, biliary sludge, and cholelithiasis.

Cholelithiasis in children with CP is diagnosed approximately 4–6 times more frequently than in the general pediatric population. The risk of stone formation progressively increases with patient age, duration of immobilization, and length of anticonvulsant therapy. Children receiving long-term enteral tube feeding constitute a particular high-risk group, in whom disruption of enterohepatic bile acid circulation is virtually constant.

1.2. Pathogenetic Mechanisms

Disorders of bile secretion in CP are multifactorial in nature. A key role is played by autonomic dysfunction caused by damage to central regulatory structures — the hypothalamus, brainstem, and diencephalic region. Normal gallbladder motility is maintained by the coordinated activity of the sympathetic and parasympathetic nervous systems, and when this is disrupted, gallbladder hypotonia or dyskinesia, bile stasis, and alterations in bile composition arise.

Spasticity of the anterior abdominal wall muscles creates an additional mechanical factor: increased intraabdominal pressure disrupts normal gallbladder anatomy and impedes its adequate emptying. This mechanism is particularly pronounced in spastic diplegia and tetraplegia — forms of CP associated with the greatest degree of motor restriction.

A significant contribution to biliary system pathology is made by disruption of the enterohepatic circulation of bile acids, caused by slowed intestinal transit. In CP, chronic constipation and small intestinal motility disorders are virtually universal, affecting, by various estimates, 60–90% of patients. Slowed transit prolongs the period of contact between bile acids and bacteria, alters their deconjugation, disturbs the pool of secondary bile acids, and creates conditions for lithogenesis.

In recent years, the relationship between impaired intestinal permeability, dysbiosis, and the state of the biliary system through the gut–liver–brain axis has been intensively studied. In children with severe forms of CP, alterations in the intestinal microbiota composition have been described, with predominance of

proinflammatory taxa, reduced levels of short-chain fatty acids, and increased intestinal permeability. These changes likely contribute to systemic inflammation, activation of Kupffer cells in the liver, and perpetuation of chronic neuroinflammation.

2. FACTORS COMPLICATING DIAGNOSIS

2.1. Communication Deficit and Atypical Clinical Presentation

One of the most significant causes of delayed diagnosis of biliary pathology in children with CP is the marked limitation of communicative abilities. According to various authors, 25–40% of children with CP are incapable of verbal communication, and in a substantial proportion of those who retain verbal communication, the level of informativeness is insufficient for precise localization of pain sensations. As a result, complaints of abdominal discomfort are either not expressed at all, or manifest as nonspecific behavioral reactions — restlessness, sleep disturbances, increased spasticity, and refusal to eat.

The atypicality of the pain syndrome is compounded by central disturbances of nociception. Pathological brain activity in CP alters the perception, integration, and expression of pain stimuli. Studies using pain scales adapted for nonverbal patients (FLACC, r-FLACC, NCCPC) demonstrate systematic underestimation of pain intensity by staff and parents.

2.2. Iatrogenic Factors: The Role of Anticonvulsant Therapy

Epilepsy is one of the most frequent comorbidities in CP: by various estimates, it occurs in 35–60% of patients. Virtually all such children receive long-term anticonvulsant therapy, which itself exerts a significant influence on the state of the biliary system.

Valproic acid — the most widely used anticonvulsant in this group — possesses dose-dependent hepatotoxicity and can cause impaired bile acid synthesis, microvesicular steatosis, and, in rare cases, fulminant hepatic failure. Carbamazepine and phenobarbital are potent inducers of cytochrome P450, which alters bile acid and fat-soluble vitamin metabolism, affecting bile composition and the risk of cholelithiasis. Long-term use of valproates is associated with the development of cholelithiasis in children, although the precise mechanisms of this relationship require further investigation.

Beyond direct hepatobiliary effects, anticonvulsants cause deficiency of folates, vitamin D, and carnitine, which exerts an indirect influence on liver function and bile composition. Routine monitoring of hepatic enzymes during anticonvulsant therapy is frequently limited to assessment of ALT and AST, without analysis of markers of cholestasis and biliary tract function.

2.3. Nutritional Deficiency and Enteral Nutrition

Nutritional disorders in CP are systemic in nature and affect the vast majority of patients with severe forms of the disease. Dysphagia, swallowing disorders, gastroesophageal reflux, delayed gastric emptying, and chronic constipation form a vicious cycle leading to protein-energy malnutrition and micronutrient deficiencies. Many children receive gastrostomy or nasogastric tube feeding.

Prolonged parenteral or tube feeding — bypassing the physiological digestive stimuli (above all, cholecystokinin secretion in response to fat entering the

duodenum) — leads to reduced gallbladder contractility, bile stasis, and biliary sludge formation. In children receiving long-term gastrostomy feeding, the frequency of biliary sludge and cholelithiasis detected on ultrasound substantially exceeds population-level rates.

2.4. Organizational and Technical Barriers

The practical conduct of diagnostic investigations in children with CP is associated with considerable organizational difficulties. Standard ultrasound examination of the gallbladder requires a fasting state and a degree of patient cooperation — conditions that in children with severe motor and behavioral disorders are frequently unachievable without sedation. Spastic contractures, fixed deformities of the spine and hip joints restrict the availability of an acoustic window.

At the healthcare system level, the problem is compounded by insufficient awareness among primary care physicians of the high frequency of biliary pathology in children with CP. Gastroenterological evaluation in CP is frequently deferred in favor of neurological and orthopedic concerns, and no standardized protocols for biliary screening in this population exist.

Table 1. Major barriers to timely diagnosis of biliary system pathology in children with CP

Barrier	Manifestation	Clinical Consequence
Communication deficit	Inability to report pain or discomfort	Delayed medical consultation
Abdominal wall spasticity	Atypical clinical presentation of abdominal syndrome	Diagnostic errors, delayed initiation of therapy
Autonomic dysregulation	Impaired gallbladder and gastrointestinal motility	Chronification of dyskinesia, risk of cholelithiasis
Polypharmacy	Anticonvulsant hepatotoxicity, altered bile rheology	Secondary cholestasis, cholelithiasis
Nutritional deficiency	Protein-energy deficit, impaired enterohepatic circulation	Reduced bile acid synthesis, dyscholia
Limited access to ultrasound	Positioning difficulties, poor compliance during examination	Underdiagnosis of structural gallbladder changes

3. DIAGNOSTIC APPROACHES AND THEIR LIMITATIONS

3.1. Ultrasound Examination

Abdominal ultrasound remains the primary imaging modality for the biliary system in children with CP owing to its safety, accessibility, and absence of radiation

exposure. The standard protocol includes assessment of gallbladder size, shape, wall thickness, and contents, as well as the state of the bile ducts. Dynamic cholecystography with a fatty meal or cholecystokinin administration allows assessment of gallbladder contractile function.

Limitations of the method in this patient population are related to the technical difficulties described above, as well as the fact that functional motility disorders may have no structural ultrasound equivalents at early stages. Normal gallbladder dimensions and echogenicity do not exclude clinically significant dyskinesia. Furthermore, interpretation of results in children receiving tube feeding requires consideration of the feeding regimen, since continuous nutritional support eliminates postprandial stimuli for gallbladder contraction.

3.2. Laboratory Diagnostics

Standard biochemical screening for suspected biliary pathology includes determination of ALT, AST, GGT, alkaline phosphatase, and total and direct bilirubin. However, in children with CP the interpretation of these parameters is substantially complicated. Alkaline phosphatase activity is physiologically elevated in the pediatric age group and rises further in the context of bone disorders (osteoporosis, fractures), which are extremely common in this population. GGT is a more specific marker of cholestasis, but is also elevated by a number of anticonvulsants.

Total serum bile acids — a relatively accessible laboratory test — allow assessment of the degree of impairment of enterohepatic circulation and hepatocyte function. In CP this marker has been virtually unstudied, making it a promising subject for clinical investigation.

3.3. Prospective Biomarkers

Over the past decade, circulating protein markers capable of reflecting the functional state of the gut–liver–brain axis have been actively investigated. Of particular interest are the following compounds.

FGF19 (fibroblast growth factor 19) is an enterokine synthesized by enterocytes of the ileum in response to bile acid absorption. FGF19 is the primary regulator of hepatic bile acid synthesis via negative feedback through the FGFR4 receptor. In an experimental model of CP, administration of recombinant FGF19 restored skeletal muscle and locomotor function, indicating neurotrophic properties of this factor. Clinical studies of FGF19 levels in children with CP are absent — a substantial research gap. The primary limitation to routine application is the absence of standardized commercial analyzers.

FGF21 is a related ligand synthesized predominantly in the liver. Unlike FGF19, commercial ELISA systems for its determination are widely available. FGF21 reflects the state of mitochondrial function, hepatic and muscle energy metabolism. In children with primary mitochondrial diseases, FGF21 levels are consistently elevated. Given the commonality of mitochondrial dysfunction pathogenetic mechanisms in severe forms of CP, FGF21 appears to be a promising candidate biomarker.

GDF15 (growth differentiation factor 15) is a cytokine of the TGF- β superfamily secreted in response to cellular stress, mitochondrial dysfunction, and

neuroinjury. Notably, elevation of GDF15 levels in the cerebrospinal fluid has been documented specifically in patients with CP, whereas systemic (serum) studies in this population are virtually absent. GDF15 crosses the blood–brain barrier and exerts neuroprotective effects, making it a potentially significant link between biliary pathology and neuroinflammation.

4. CLINICAL CONSEQUENCES OF DELAYED DIAGNOSIS

Untimely detection of biliary system pathology in children with CP entails a spectrum of clinical consequences extending well beyond gastroenterology proper. Chronic pain syndrome in unrecognized biliary pathology manifests as nonspecific behavioral restlessness, sleep disturbances, increased spasticity, and reduced rehabilitation capacity. In pediatric neurorehabilitation centers, it is not uncommon for deterioration in motor performance in a child with CP to be attributed to progression of the underlying disease, whereas the true cause is unrelieved abdominal pain syndrome.

Worsening nutritional deficiency in the context of biliary pathology forms a vicious cycle: impaired fat digestion exacerbates deficiency of fat-soluble vitamins (A, D, E, K), impairs absorption of essential fatty acids required for myelination, and reduces the effectiveness of nutritional support. In children with CP receiving tube feeding, these disturbances may remain undetected against a background of formally satisfactory anthropometric parameters.

From the perspective of the gut–liver–brain axis, chronic cholestasis and impaired enterohepatic circulation of bile acids potentially sustain systemic and neuroinflammation. Bile acids possess direct neuromodulatory effects — they penetrate the compromised blood–brain barrier and interact with TGR5 and FXR receptors in brain cells. Chronic elevation of secondary bile acid concentrations in the systemic circulation may enhance astroglial activation, which theoretically is reflected in elevated S100B and GFAP — recognized markers of neuroinflammation in CP.

5. DIRECTIONS FOR IMPROVING DIAGNOSTICS

5.1. Screening Protocols

Existing clinical guidelines for the management of children with CP generally do not include structured algorithms for biliary screening. Yet the high prevalence of this pathology in the population and the severity of its consequences justify the need to develop and implement specialized diagnostic protocols. It appears appropriate to include scheduled biliary tract sonography in the standard annual examination for children with CP at GMFCS levels III–V, as well as when anticonvulsant therapy is initiated or changed.

A laboratory screening algorithm for biliary pathology in children with CP should include: a biochemical blood panel with mandatory determination of GGT, direct bilirubin, and bone-specific alkaline phosphatase fraction; total serum bile acids; fat-soluble vitamins (D, E, K); and assessment of nutritional status with calculation of malnutrition indices. Screening frequency should be determined by the severity of motor impairment and pharmacological burden.

5.2. Adaptation of Diagnostic Methods

Technical difficulties in performing ultrasound in children with CP may be partially overcome through the use of adapted positioning protocols, with pharmacological sedation when necessary. Use of functional tests with cholecystokinin or a standardized fatty meal enhances the diagnostic value of the examination by enabling assessment of gallbladder contractile function.

For assessment of pain and discomfort in nonverbal patients, systematic use of validated instruments is required — including the r-FLACC scale, Pediatric Pain Profile (PPP), and analogous tools. Development of standardized observation charts for behavioral changes reflecting abdominal discomfort will improve the informativeness of clinical assessment.

5.3. Multidisciplinary Approach

Optimal management of children with CP involves close collaboration among neurologist, gastroenterologist, dietitian, rehabilitation specialist, and pediatrician. Regular multidisciplinary consultations allow integration of data on pharmacological burden, nutritional status, and instrumental examination results to enable timely identification of biliary pathology. An important role is played by education of parents and caregiving staff in the observation of behavioral pain markers.

CONCLUSION

Biliary system pathology is a substantially underestimated comorbidity in children with cerebral palsy. Its timely diagnosis is impeded by a complex of interrelated factors: limitations in patients' communicative abilities, atypicality of clinical manifestations, hepatobiliary effects of anticonvulsant therapy, nutritional deficiency, autonomic dysregulation of gallbladder motility, and organizational barriers.

Existing diagnostic tools — ultrasonography and standard biochemistry — retain their value but are insufficient for early functional diagnosis and monitoring. Promising directions include the introduction of total bile acids into routine screening, and the investigation of circulating markers of the gut–liver–brain axis (FGF21, GDF15) as potential biomarkers for this population.

Addressing this problem requires the development of standardized screening protocols, adapted diagnostic algorithms, and implementation of a multidisciplinary approach within the specialized care system for children with CP. Clinical studies devoted to assessment of the prevalence, clinical features, and biomarkers of biliary pathology in CP represent an urgent task for pediatric gastroenterology and neurology.

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