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NEUROLOGY OF SYSTEMIC DISEASES (J. BILLER, SECTION EDITOR)

Bilirubin Encephalopathy

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Abstract

Purpose of Review Hyperbilirubinemia is commonly seen in neonates. Though hyperbilirubinemia is typically asymptomatic, severe elevation of bilirubin levels can lead to acute bilirubin encephalopathy and progress to kernicterus spectrum disorder, a chronic condition characterized by hearing loss, extrapyramidal dysfunction, ophthalmoplegia, and enamel hypoplasia. Epidemiological data show that the implementation of universal pre-discharge bilirubin screening programs has reduced the rates of hyperbilirubinemia-associated complications. However, acute bilirubin encephalopathy and kernicterus spectrum disorder are still particularly common in low- and middle-income countries.

Recent Findings The understanding of the genetic and biochemical processes that increase the susceptibility of defined anatomical areas of the central nervous system to the deleterious effects of bilirubin may facilitate the development of effective treatments for acute bilirubin encephalopathy and kernicterus spectrum disorder. Scoring systems are available for the diagnosis and severity grading of these conditions. The treatment of hyperbilirubinemia in newborns relies on the use of phototherapy and exchange transfusion. However, novel therapeutic options including deep brain stimulation, brain-computer interface, and stem cell transplantation may alleviate the heavy disease burden associated with kernicterus spectrum disorder.

Summary Despite improved screening and treatment options, the prevalence of acute bilirubin encephalopathy and kernicterus spectrum disorder remains elevated in low- and middle-income countries. The continued presence and associated long-term disability of these conditions warrant further research to improve their prevention and management.

Keywords Hyperbilirubinemia · Bilirubin encephalopathy · Bilirubin-induced neurotoxicity · Kernicterus spectrum disorder

Introduction

Bilirubin is an endogenous yellowish pigment that results from the metabolism of the heme group contained in red blood cells (Fig. 1). Neonatal hyperbilirubinemia is common and mostly benign, manifesting with jaundice which is typically observed in the first week of life. Based on observational studies, it has been estimated that 60% of term and 80% of preterm neonates experience hyperbilirubinemia [1, 2]. The term bilirubin encephalopathy (BE) refers to the acute and chronic neurological dysfunction seen in association with severe hyperbilirubinemia. Extremely elevated levels of total bilirubin (TB ≥ 25 mg/dL) can lead to acute bilirubin encephalopathy (ABE) and cause significant morbidity or mortality if not adequately treated. Survivors often experience long-term neurologic deficits ranging from mild movement disorders and/or auditory dysfunction to severe choreoathetoid cerebral palsy, auditory neuropathy, and gaze palsies [3]. In the next sections, we discuss the epidemiology, clinical features, pathogenesis, and treatments of BE.

Terminology and Epidemiology

Several terms have been adopted to describe bilirubin neurotoxicity including BE, ABE, kernicterus, chronic bilirubin encephalopathy, and bilirubin-induced neurological dysfunction (BIND). The term "kernicterus" has been used interchangeably for both acute and chronic bilirubin-induced neurotoxicity since its conception in 1903 by pathologist

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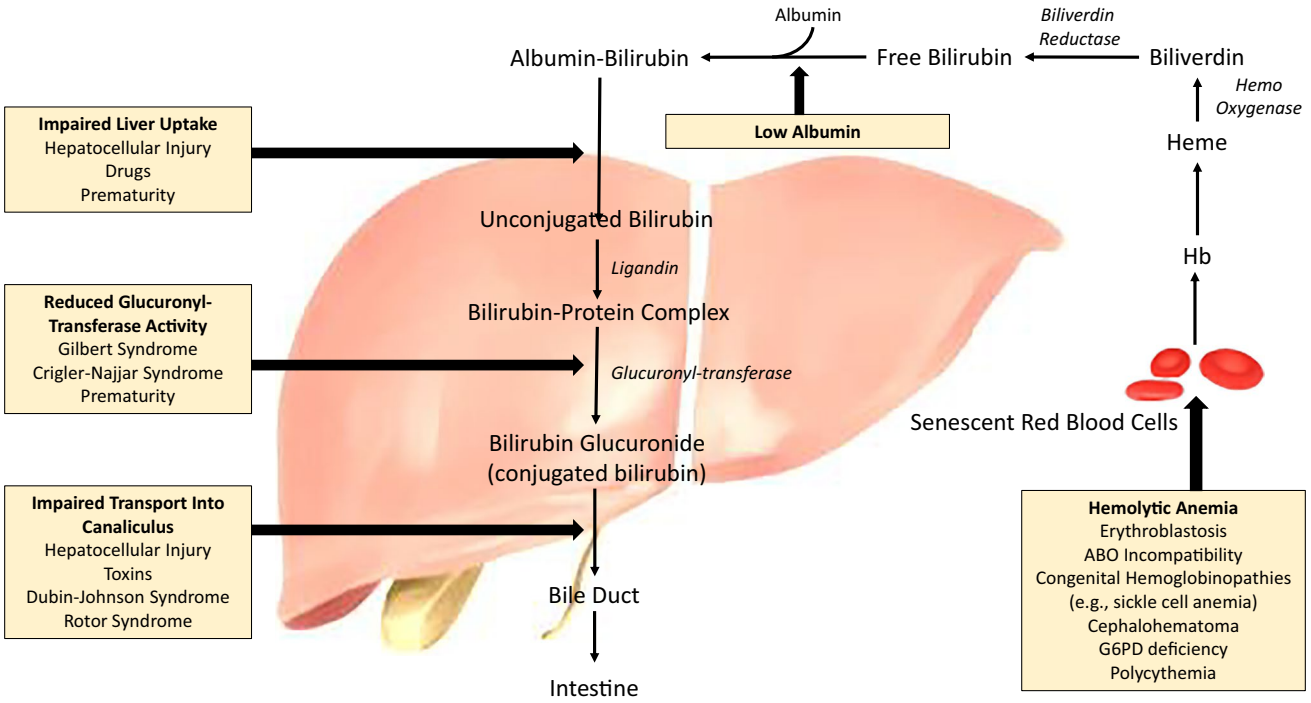

Fig. 1 Metabolism of bilirubin. Bilirubin originates primarily from the senescence of circulating red blood cells. Heme, a protoporphyrin ring that functions as a prosthetic group in hemoglobin (Hb), is sequentially metabolized to biliverdin and bilirubin. In physiologic conditions, more than 99% of the unconjugated bilirubin in the circulation is bound to albumin and only a small portion remains as free bilirubin which is liposoluble and can cross the blood–brain barrier. In the liver, bilirubin is conjugated with glucuronic acid which is water soluble and excreted into the biliary track and the intestine. Hyperbilirubinemia in the neonate can result from overproduction of bilirubin (hemolytic anemia), low availability of albumin, reduced UDP-glucuronyltransferase activity, or impaired excretion

Christian Schmorl, who used it to describe the post-mortem findings of yellow staining of the basal ganglia (BG), hippocampus, and central parts of the cerebellum [4]. To avoid confusion, in 2004, the American Academy of Pediatrics (AAP) recommended to use the term ABE for the manifestations of bilirubin neurotoxicity seen in the first weeks after birth, and "kernicterus" for the chronic and permanent clinical sequelae [5]. Le Pichon JB et al. further suggested to replace all the terms previously used for chronic BE with "kernicterus spectrum disorder" (KSD) to encompass the gamut of long-term neurological sequelae resulting from BE [6•]. In this review, we use ABE and KSD to describe the acute- and long-term consequences of bilirubin neurotoxicity, respectively, and BE as a more generic term that encompasses ABE and KSD.

The epidemiology of BE varies significantly across the globe and the population investigated. In general, the prevalence for kernicterus in high-income countries is estimated as 10/100,000 live births. However, the implementation of universal pre-discharge bilirubin screening programs and the early treatment of hyperbilirubinemia has reduced the rate of complications associated with it. As an example, data from the Healthcare Cost and Utilization Project Kids' Inpatient Database (KID) for the years 1997–2012 show that the proportion of infants diagnosed with hyperbilirubinemia increased from 9.4 to 15.5% during the study period. In parallel, the rate of discharges with the diagnosis of kernicterus decreased from 7 to 1.9 per 100,000 newborns [7]. In comparison, the rate of kernicterus in low- and middle-income countries (LMIC) has remained particularly elevated, with a prevalence of approximately 73/100,000 live births reported in Eastern Europe/Central Asia, Latin America, sub-Saharan Africa, and South Asia [8].

Risk factors for neurotoxicity from extreme hyperbilirubinemia include central nervous system (CNS) prematurity, hemolytic disease due to blood group incompatibility, inherited red blood cell enzymatic deficiencies or membrane defects (e.g., glucose-6-phosphate dehydrogenase deficiency), genetic predisposition, and medical conditions such as sepsis, intracranial hemorrhage, and acidosis (Fig. 1) [9, 10•]. There are also multiple reports describing delayed presentation of BE without a history of ABE during the first days of life which suggests that additional unknown risk factors may play a role in the disease.

Clinical Manifestations

ABE has been categorized into three phases with variable onset. Phase 1 or early ABE is typically seen during the first 1–3 days of the illness and is characterized by nonspecific symptoms of decreased alertness, poor feeding and sucking, mild hypotonia, and hyperreflexia. Phase 2 or intermediate ABE usually presents by the end of the first week with stupor, irritability, and hypertonia of extensor muscles resulting in opisthotonos, retrocollis, and high-pitched cry. Phase 3, also known as late or advanced ABE, is seen after the first week and is characterized by hypotonia or hypertonia, pronounced opisthotonos-retrocollis and high-pitched crying, apnea, deep stupor or coma, fever, and sometimes seizures [11•, 12•].

KSD, which refers to the chronic and enduring clinical consequences of bilirubin toxicity, may develop slowly over years in some children that survive ABE. During the first year, decreased muscle tone, increased deep tendon reflex, delayed achievement of developmental milestones and motor skills, and persistent tonic neck reflex are present [12•]. After the first year, the clinical manifestations are often variable and classically represented by the tetrad of hearing loss, motor (extrapyramidal) dysfunction, ophthalmoplegia, and enamel hypoplasia. Auditory and motor symptoms are the most salient features leading to disability. Damage of auditory networks manifests as auditory neuropathy spectrum disorder (ANSD) [13]. This is one of the earliest features of KSD and can often be the only clinical manifestation. Rather than sensorineural dysfunction, ANSD is characterized by absent or diminished auditory brainstem responses, sometimes accompanied by auditory nerve dysfunction sparing the cochlea and hair cells [14–17]. Children suffering from ANSD may have pure tone thresholds ranging from mild to profound hearing loss and experience reduced speech perception, leading to an inability to perform sound localization or speech discrimination [18, 19]. Extrapyramidal dysfunction presents largely as dystonia and choreoathetosis [20]. The presentation of movement disorders is variable but the upper extremities are typically more severely affected. Rapid and jerky movements, tremors, ballismus, and dystonic posturing are common [12•]. Visual abnormalities include upward gaze paresis, horizontal gaze dysfunction, and a blank stare or "scared" appearance resulting from the upward gaze paresis and facial dystonia. Dental abnormalities are relatively uncommon and include dental enamel hypoplasia and green-stained teeth [21]. Cognitive function is typically preserved in children with KSD.

Pathophysiology

BE results from the deposition of unconjugated bilirubin (UCB), particularly free bilirubin (B_f) in specific anatomical areas of the CNS, including the brainstem nuclei, BG, thalamus, hippocampus, and cerebellum [22, 23, 24•]. The mechanism of bilirubin-induced neurotoxicity is incompletely understood. However, post-mortem and animal studies suggest the active role of neuroinflammation, excitotoxicity, mitochondrial failure, and DNA damage [11•, 25].

Hyperbilirubinemia itself results from the imbalance of the production and excretion of bilirubin. Infants have high turnover of red blood cells [26] with limited ability to conjugate bilirubin. While most neonatal hyperbilirubinemias are physiologic and rarely exceed 5 to 6 mg/dL, pathologic jaundice may occur due to increased production of bilirubin, deficiency of hepatic uptake, impaired conjugation of bilirubin, or increased enterohepatic circulation of bilirubin [21]. This can lead to the accumulation of UCB and B_f, the latter being a lipid-soluble compound that can cross the blood–brain barrier (BBB) [15]. B_f has a cytotoxic effect on astrocytes and neurons, resulting in microglial and astrocyte activation, impaired myelination, and neuronal death [27–29]. Its accumulation in the CNS and cerebrospinal fluid is mediated by transporters in the choroid plexus epithelia, endothelial cells, astrocytes, and neurons [30]. B_f increases significantly when UCB approaches the maximum binding capacity of albumin (1 g of albumin can bind 8 mg of bilirubin, ~ 1:1 on a molar basis) [31]. Whether bilirubin-induced neurotoxicity occurs or not depends on different variables, including serum UCB and albumin levels, bilirubin binding capacity by albumin, concentration of hydrogen ions, BBB function, neuronal susceptibility, and degree of CNS maturity, as well as the duration and severity of the hyperbilirubinemia [32–34].

Proposed molecular mechanisms of bilirubin-induced neurotoxicity involve excessive glutamate release, upregulation of proinflammatory cytokines, mitochondrial failure, and DNA damage [11•, 25]. Bilirubin-induced impairment of membrane transporters in astrocytes and neurons causes an increase and prolonged presence of the excitatory neurotransmitter glutamate in the synaptic cleft [35]. Cytokines such as tumor necrosis factor alpha and interleukin-1β released by astrocytes may be involved in this process [36]. Excessive glutamate results in overstimulation of neuronal N-methyl D-aspartate (NMDA) receptors causing an increased influx of sodium, calcium, chloride, and water, generating free radicals and triggering cell death by necrosis or apoptosis [37–40]. UCB can also interact with nerve cell membranes causing oxidative damage and increased permeability, compromising lipoprotein structure and eventually disrupting cell homeostasis [41]. Furthermore, UCB can impair oxidative phosphorylation in mitochondria, leading to decreased energy production and increased mitochondrial permeability resulting in swelling and release of cytochrome C into the cytosol [30]. The subsequent activation of caspase-3 (an executioner caspase) and translocation of Bax [42] activate

mitochondrial-mediated pro-apoptotic pathways. In addition, caspase 8 (an initiator of apoptosis) may be activated as well, implicating the participation of cell-surface death receptor pathways [43]. Novel mechanisms have been more recently described. To this end, using a mouse model of neonatal hyperbilirubinemia, Rawat V et al. described that DNA injury via bilirubin-induced oxidative stress can also contribute to neuronal death and BE. In addition, it was observed that bilirubin activates main DNA repair pathways through homologous recombination and nonhomologous end joining, suggesting that these may constitute endogenous protective mechanisms against BE [25].

Data obtained in human and animal models have demonstrated that the brainstem nuclei, BG, hippocampus, and cerebellum are particularly sensitive to the detrimental effects of bilirubin [44–52]. Affected brainstem nuclei include auditory (cochlear, superior olivary, trapezoid body, lateral lemniscus, inferior colliculi), oculomotor, and vestibular nuclei [24•]. Auditory networks appear to be particularly sensitive to bilirubin toxicity and primarily involve brainstem nuclei and cranial nerve VIII. Bilirubin deposition in the BG, particularly the globus pallidus and subthalamic nuclei, as well as in the cerebellar Purkinje cells, likely causes the motor symptoms of BE [22, 48, 49]. The hippocampal CA2 region is another commonly affected structure, and the inhibition there of long-term potentiation of synaptic transmission consequently affects learning and memory [53].

Gazzin et al. conducted a study using the jj-sulfa Gunn rat model of hyperbilirubinemia and observed greater accumulation of UCB in the cerebellum and inferior colliculi, along with lesser accumulation in other "resistant" areas including the cortex and superior colliculi, of which functionality (cognition and vision, respectively) is usually preserved in kernicterus [54]. Several theories have been proposed to address this regional gradient in the accumulation of bilirubin. One hypothesis suggests a role of parvalbumin (PV), a calcium-binding protein [24•], due to decreased PV immunoreactivity in brainstem nuclei of dystonic jj-sulfa Gunn rats with severe kernicterus [50, 51]. As 95% of the neurons in the globus pallidus are GABAergic and 50–60% co-express PV, Shapiro et al. suggest that degeneration of PV-GABAergic neurons may be the most important cause of kernicterus-associated dystonia [55–58]. Another theory involves multi-drug resistance P-glycoproteins and multidrug resistance–associated proteins (MRPs/Mrps), two large families of ATP-binding cassette transporters that mediate the export of compounds that may be toxic for the brain, including perhaps UCB [59]. There is evidence supporting the role of MRP1/Mrp1 in maintaining intracellular homeostasis and protection of CNS cells against UCB accumulation and toxicity. It has been hypothesized that variations in the expression and/or function of MRP1 may explain regional selectivity to UCB toxicity and differences in the severity of BE among neonates [30].

New technological advances have allowed the identification of genetic variations that contribute to bilirubin-induced neurotoxicity. The genes UGT1A1 and SLCO1B1 have been implicated in abnormal bilirubin processing [60, 61]. Also, cytochrome P450 monooxygenases (Cyps) are proteins that oxidize bilirubin. Studies have confirmed upregulated mRNA expression of Cyp1a1, Cyp1a2, and Cyp2a3 in neurotoxicity-resistant regions of the brain as compared to more sensitive regions, suggesting a potential protective effect of these isoforms [54]. Data obtained in experimental models, in addition, show that UCD activates microglial cells which exert an early neuroprotective effect by clearing damaged neurons. In a later stage, however, microglial cells secrete pro-inflammatory mediators which have a direct effect on astrocytes. Together, microglial cells and activated astrocytes contribute to the production of additional inflammatory mediators which are cytotoxic and enhance astrogliosis. Furthermore, UCB can compromise myelinogenesis and axonal transmission directly or via microglial cells [36, 62–66]. Understanding the genetic and biochemical mechanisms that govern these responses can help us explain the different clinical manifestations observed in patients with similar bilirubin levels, and may also help us identify infants at high risk of developing permanent brain damage [24•, 67].

Diagnosis

Historically, the diagnosis of BE relied on identification of the aforementioned autopsy findings. In contemporary practice, however, the diagnosis of ABE or KSD can be made with reasonable certainty using the combination of medical history, physical examination, laboratory testing, clinical scoring systems, neurophysiological studies, and neuroimaging. Relevant history includes symptom onset and duration and history of risk factors such as CNS immaturity, hemolytic disease, family history of anemia or jaundice, and neurotoxic factors such as sepsis, acidosis, and intracerebral hemorrhage. Hyperbilirubinemia severity and duration, along with a detailed clinical examination, are also important for the diagnosis.

Jaundice alone is a suboptimal screening tool to detect hyperbilirubinemia. Thus, many countries have implemented universal screening of bilirubin levels [68]. Total plasma or serum bilirubin levels were classically determined in the laboratory by measuring the absorbance at 460 nm. Newer approaches, such as the BR2 Bilirubin Stat Analyzer from Advanced Instruments (Norwood, MA), can determine total and direct bilirubin levels in neonates using samples of only 30 µL. In addition, noninvasive transcutaneous bilirubin (TcB) readers are now widely available in most high-income countries. Studies have shown a strong correlation between

TcB and TB measurements in both term [69, 70] and preterm newborns [71, 72], although serum albumin levels and phototherapy may impact the accuracy of this technique [73, 74]. In addition, new point-of-care instruments such as two-color icterometers (Bilistrip™) [75] and smartphone-based methods (BiliCam) [76] can help mothers and healthcare providers make the initial determination of whether a child needs to be seen by a physician. Free bilirubin is classically measured by the "peroxidase method," a methodology that is not widely available and considered exceedingly challenging for most clinical laboratories to perform. However, new technological advances, including the use of fluorescent sensors, may soon facilitate the accurate determination of B_f [77, 78].

Auditory involvement in BE can be assessed non-invasively by auditory brainstem responses (ABR). It has been proposed that ABR has a sensitivity of 100% and a specificity of 99.4% for detecting auditory involvement [12•]. Patients typically have abnormal or absent ABRs, with normal or giant cochlear microphonic responses and varying otoacoustic emissions [6•]. It is possible that in the near future, new technologies become available that are specifically designed to improve the diagnosis of BE and predict the risk and severity of KSD. These could include the determination of genetic risk by using a "bilirubin risk chip" or the assessment of CNS function by using fully automated neurophysiologic approaches, such as the modern "next gen" ABR technology.

Clinical scoring systems have been designed to aid in the diagnosis and grading of BE. The BIND [79] and modified BIND (BIND-M) scores (Table 1) [80] have been validated and widely adopted in clinical practice. The BIND score evaluates mental status, muscle tone, and cry characteristics to delineate three levels of ABE: subtle (1–3), moderate (4–6), and advanced (7–9). The BIND-M score additionally incorporates possible upward gaze paresis. A BIND-M score ≥ 3 was highly predictive of a clinical diagnosis of ABE, with a sensitivity of 90.7% and specificity of 97.7% [80]. Scores 1–4, 5–6, and 7–12 represent mild, moderate, and severe ABE, respectively. The BIND-M helps differentiate ABE from other causes of jaundice with similar clinical presentations. The KSD scoring system, based on the KSD Diagnostic Toolkit (KSD-TK) (Tables 2 and 3), allows a better characterization and grading of KSD [6•]. This scoring system focuses on motor and auditory disabilities as these are considered clinically significant and quantifiable features of BE. The identification and grading of clinical features such as oculomotor dysfunction can be challenging, and dental enamel dysplasia is rarely present. In a retrospective study including 37 patients, KSD-TK had 96.6% sensitivity and 87.5% specificity [6•, 81].

Finally, magnetic resonance imaging (MRI) has been shown to improve accuracy of diagnosis in BE. In ABE, MRI commonly shows bilateral T1 hyperintensity of the globus pallidus [82–84], and one study demonstrated significant correlation between bilirubin levels and apparent diffusion

Table 1 Modified bilirubin-induced neurologic dysfunction (BIND-M) score

	Score
Mental status	
• Normal	0
• Sleepy but arousable or decreased feeding	1
• Lethargy, poor suck, and/or irritable/jittery with short-term strong suck	2
• Stupor, apnea, seizures, or coma	3
Muscle tone	
• Normal	0
• Persistent mild hypotonia	1
• Moderate hypotonia, moderate hypertonia, or increasing arching of neck and trunk on stimulation without spasms of arms and legs and without trismus	2
• Persistent retrocollis, opisthotonus, or crossing or scissoring of arms or legs but without spasms of arms and legs and without trismus	3
Cry pattern	
• Normal	0
• High pitched	1
• Shrill	2
• Inconsolable crying or either weak or absent in child with previous history of high pitched or shrill cry	3
Oculomotor or eye movements	
• Normal	0
• Sun-setting or paralysis of upward gaze	3

Table 2 Kernicterus spectrum disorder (KSD) toolkit scoring system

Symptoms	Severity	Characteristics	Score
Auditory	None	No auditory symptoms	0
	Mild	ABR abnormal but present or CAPD ± mild hearing loss; normal or mildly delayed speech	1
	Moderate	Absent or persistent abnormal ABR, mild/moderate hearing loss, may fluctuate; speech delayed or absent	2
	Severe	Absent ABR, severe-to-profound hearing loss/deafness	3
Motor	None	No motor symptoms	0
	Mild	Mild abnormal muscle tone ± athetosis; mild gross motor delay	1
	Moderate	Moderate abnormal muscle tone ± athetoid cerebral palsy; able to ambulate with or without assistance	2
	Severe	Severe abnormal tone ± athetoid cerebral palsy; unable to ambulate, feed self, sign, speak; often with episodes of severe increased tone and muscle cramps	3

ANSD, auditory neuropathy spectrum disorder; *ABR*, auditory brainstem response; *CAPD*, central auditory processing disorder

Table 3 Kernicterus spectrum disorder (KSD) severity and type

		Auditory symptoms or severity			
		None	Mild	Moderate	Severe
Motor symptoms or severity	None	None	Mild auditory	Moderate auditory	Severe auditory
	Mild	Mild motor	Mild motor and auditory	Mild motor, moderate auditory	Mild motor, severe auditory
	Moderate	Moderate motor	Moderate motor, mild auditory	Moderate motor and auditory	Moderate motor, severe auditory
	Severe	Severe motor	Severe motor, mild auditory	Severe motor, moderate auditory	Severe motor and auditory

coefficients (ADC) [85]. In 2021, Wu et al. showed that the accuracy of the diagnosis of ABE can be improved by using deep learning algorithms involving multimodal MRI with the combination of T1- and T2-weighted imaging, ADC, and convolutional neural networks [86]. In comparison, children with KSD often show increased T2 signals of the globus pallidus, especially in cases having significant motor symptoms [15, 87, 88].

Management

Phototherapy and exchange transfusion (ET) are the mainstay of treatment for hyperbilirubinemia in newborns. Phototherapy, which has been used for over half a century to treat newborns with jaundice, reduces the levels of UCB regardless of its etiology [89]. When exposed to light, a fraction of parenchymal and circulating bilirubin undergoes configurational isomerization (reversible), structural isomerization (irreversible), and photooxidation [90]. Though phototherapy does not address the underlying cause of hyperbilirubinemia, it can effectively lower UCB levels and ameliorate the severity of the symptoms [91]. ET is typically used for severe neonatal hyperbilirubinemia unresponsive to phototherapy [92]. Guidelines for the use of these two treatments in term [5, 68], preterm, and low-birth-weight infants have been published elsewhere [93, 94]. In addition, the use of intravenous immune globulin has been shown to reduce the need for exchange transfusions in Rh and ABO hemolytic disease and is recommended if TB levels continue to rise despite intensive phototherapy or remain within 2 to 3 mg/dL of the exchange transfusion level [95]. Other treatment strategies, such as pharmacologic treatment using tin-mesoporphyrin [96–99], minocycline [100–102], or caffeine [103], and therapeutic hypothermia [104], may reduce the severity of BE and are currently under investigation.

Regarding treatment of long-term sequelae, patients with ANSD may benefit from strategies such signal-to-noise ratio maximization with "FM-listening" devices and sound amplification through conventional hearing aids or cochlear implants [105]. For patients with moderate to severe motor dysfunction, symptomatic treatment relies on the use of benzodiazepines, baclofen, trihexyphenidyl (anticholinergic), and tetrabenazine (antidopaminergic). Botulinum toxin injection and intrathecal baclofen are sometimes offered to patients with severe and refractory symptoms. There is anecdotal evidence supporting the use of valbenazine or cannabinoid oil [106•], but high-quality clinical trials in this area have not been conducted. Similarly, the use of deep brain stimulation targeting the globus pallidus interna [107] has

shown promising results in patients with secondary dystonia due to KSD. However, larger studies are needed to confirm the efficacy and sustainability of this approach. Other therapeutics under investigation for the treatment of severe motor dysfunction include brain-computer interface implantation [108–110] and the use of autologous stem cells [111–114].

Conclusion

More than a century has passed since the first BE case was reported. Despite ABE and KSD being preventable and treatable, the incidence of these conditions remains elevated, particularly in low- and middle-income countries. Early diagnosis and treatment of hyperbilirubinemia are the best strategies to prevent the occurrence of bilirubin-induced neurotoxicity, which can lead to long-term disability and death. Our armamentarium for the treatment of chronic neurologic complications is expanding. However, the promising results observed in small cohorts require confirmation using properly powered studies.

Compliance with Ethical Standard

Conflict of Interest Shuo Qian, Prateek Kumar, and Fernando D Testai each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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