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Disease burden of Crigler–Najjar syndrome: systematic review and future perspectives

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ABSTRACT

BACKGROUND AND AIM: Crigler–Najjar syndrome (CNS) results from biallelic mutations of *UGT1A1* causing partial or total loss of uridine 5´-diphosphate glucuronyltransferase activity leading to unconjugated hyperbilirubinemia and its attendant risk for irreversible neurological injury (kernicterus). CNS is exceedingly rare and has been only partially characterized through relatively small studies, each comprising between two and 57 patients.

METHODS: We conducted a systematic literature review to consolidate data on the patient, caregiver, and societal burden of CNS.

RESULTS: We identified 28 articles on clinical aspects of CNS, but found no published data on its humanistic or economic burden. In patients with complete UGT1A1 deficiency (type 1 CNS [CNS-I]), unconjugated bilirubin levels increase 3–6 mg/dL per day during the newborn period and reach neurologically dangerous levels between 5 and 14 days of age. Phototherapy is the mainstay of treatment, but poses significant challenges to patients and their families. Despite consistent phototherapy, patients with CNS-I have worsening hyperbilirubinemia with advancing age. Liver transplantation is the only definitive therapy for CNS-I and is increasingly associated with excellent long-term survival, but also incurs high costs, medical and surgical morbidities, and risks of immunosuppression.

CONCLUSIONS: CNS is associated with a substantial burden, even with existing standards of care. The development of novel disease-modifying therapies has the potential to reduce disease burden and improve the lives of CNS patients and their families.

Keywords: Crigler–Najjar, Clinical burden, Mortality, Transplantation, Phototherapy

INTRODUCTION

Crigler–Najjar syndrome (CNS; MIM 218800)[1] is a rare autosomal recessive disorder caused by biallelic mutations in *UGT1A1*, which encodes a uridine 5´-diphosphate glucuronyltransferase (UGT1A1) that mediates the glucuronidation of native (Z,Z) bilirubin into mostly diglucuronides with some monoglucuronide.[2–5] Serial conjugation with glucuronides renders bilirubin hydrophilic and is requisite for its excretion by the hepatobiliary system[3] (Figure 1).

Elevated levels of unconjugated bilirubin can cause a devastating encephalopathy called kernicterus[3,5]—adapted from the German *kern* ("nucleus") and *ikterus* ("jaundice")[ca. 1903]—referring to the deposition of bilirubin pigment in cranial nerve and subthalamic nuclei, basal ganglia (in particular, the globus pallidus) and the hippocampus[3,5,6] that accompanies a spectrum of irreversible neurological sequelae.[3,7–10] Historically, the severity of CNS has been roughly categorized according to residual UGT1A1 activity and its inducibility under phenobarbital exposure. Although imperfect, this allows classification into clinical variants described as type 1 (absence of UGT1A1 enzymatic activity; CNS-I), type 2 (<10% UGT1A1 enzymatic activity; CNS-II), and Gilbert syndrome (~20% UGT1A1 enzymatic activity) (MIM PS237450).[3–5]

With an estimated incidence of 1 per 750,000–1,000,000 live births (National Organization for Rare Disorders), CNS is considered an "ultra-rare orphan disease".[11] Rare disorders tend to have a high unmet need that stems from an incomplete understanding of clinical manifestations, pathogenesis, and disease progression combined with inadequate academic and industry support for the development of effective treatments.[12,13] Delays in diagnosis and the social isolation experienced by patients and families also contribute to the burden.[13]

The overall burden of any genetic disorder encompasses its clinical and economic consequences as well as its impact on patients' health-related quality of life (HRQoL), functioning, and caregivers (collectively known as the 'humanistic' burden). Our objective for the current literature review is to more fully characterize the clinical, humanistic, and economic burden of CNS attributable to both chronic hyperbilirubinemia and its extant treatments.

METHODS

A PRISMA 2009 checklist[14] and review protocol summary are provided as supporting information.

The following research questions were defined at the start of this analysis: 1) What are the clinical features and complications of CNS? 2) What is the course of disease progression in CNS and what are the associated factors? 3) What mortality has been reported in CNS and what are the associated factors? 4) What is the standard of care treatment of CNS and what is its related burden? 5) What is the impact of CNS on patient HRQoL, self-reported symptoms, activities of daily living (ADLs), caregiver burden, and treatment satisfaction and adherence? 6) What is the economic burden (healthcare resources use, utilities, direct and indirect costs) of CNS? 7) How do the humanistic and economic burden of CNS change over time? 8) What interrelationships exist between and among clinical, humanistic, and economic burden parameters in CNS?

Search strategy and selection criteria

This review involved systematic searches in Embase®/MEDLINE® using Embase.com® to identify relevant articles published through December 2017 on the clinical, humanistic, and economic burden of CNS. Each search was conducted using controlled vocabulary and key words and was limited to articles published in English and studies involving human subjects. Specific search terms used are provided as supporting information. Additional papers were identified through bibliography reviews of relevant articles. Supplementary literature searches using Google, Google Scholar and other web sources were also performed.

Titles and abstracts of articles identified were carefully screened by a single reviewer in the initial review for relevance to the topic. Articles were selected for inclusion based on predefined acceptance criteria, which included patient population (patients diagnosed with CNS), outcome measures of interest (clinical burden, humanistic burden, economic burden), and study design (quantitative and/or qualitative data collection). Exclusion criteria included non-English language and absence of peer-review for articles, editorials, correspondence, and conference abstracts.

Potentially relevant articles were obtained in full text for further evaluation. Each was screened, and its eligibility confirmed by two reviewers. Inconsistencies were resolved through consensus.

Quality assessment

A descriptive analysis of each publication was conducted during data extraction. The reviewer assessed each publication for quality by considering characteristics that could introduce bias. Quality assessment was conducted using a tool based on the design of the study: 1) Newcastle-Ottawa Scale for cohort studies and case-control studies;[15] 2) Adapted Newcastle-Ottawa Scale for cross-sectional studies;[15] 3) AMSTAR measurement tool for reviews;[16] 4) Cochrane risk of bias assessment tool for randomized controlled trials.[17]

Data extraction

Data from the included publications were extracted into a predefined extraction grid by a single reviewer as follows: study design, setting, patient characteristics, outcome measures, key results, and conclusions. Given the descriptive nature of this systematic review, extracted data were narratively synthesized.

RESULTS

Overview

Following the initial searches, we screened the titles and abstracts of 1,060 citations. Among these, 58 full-text articles were assessed for eligibility of which 28 articles were selected for analysis (Figure 2). No publications reported humanistic or economic burden of CNS, and this article therefore focuses exclusively on its clinical aspects.

Table 1 summarizes 28 studies that report on the clinical burden of CNS. Of these, three were general review articles,[2,3,8] one of which also included results of an international survey.[2] Of the remaining 25 publications, eight were case series[18–23] or case reports,[24,25] 10 were retrospective cohorts,[26–35] three were prospective cohorts,[36–38] two were randomized controlled trials (RCTs),[39,40] and two were cross-sectional studies.[7,41] Nineteen primary publications were specific to CNS,[7,18–25,29,30,32–36,39–41] while six comprised patients with various inherited metabolic disorders including CNS.[26–28,31,37,38] Most studies were conducted in Europe or the US, with others in Saudi Arabia, Turkey, Japan, and Australia.

Thirteen of the 19 CNS-specific primary publications were conducted exclusively in patients with CNS-I,[7,18–23,25,29,30,33,34,41] two were in CNS-II,[24,36] and four included patients with both clinical variants.[32,35,39,40] Description of case reports and case series is mostly confined to the summary tables. Summary values are represented as the arithmetic mean ± one standard deviation except where otherwise indicated.

Clinical burden of CNS

What are the clinical features and complications of CNS?

The primary clinical feature of CNS is unconjugated hyperbilirubinemia, which ranges from 4 mg/dL to 45.2 mg/dL[7,18–21,23,24,31,32,41] and exhibits distinctive patterns related to patient age and clinical circumstance (see below).

Neurological sequelae of CNS were variable. One international multicenter study reported neurologic impairment in 15 (26%) of 57 CNS-I patients, with signs ranging from severe intellectual disability to minor psychomotor impairments.[7] Signs of neurologic damage (e.g. cerebellar dysfunction, mild speech delay) were also reported in six (14%) of 42 CNS-I patients from a survey of 14 treating physicians.[41] In contrast, no neurological complications were reported in a retrospective study of 20 CNS patients managed over 200 patient-years of follow-up at a single center.[32] Complications of kernicterus from other studies are summarized in Table 2.

Although hearing loss is commonly considered a consequence of bilirubin encephalopathy, no CNS-I patients from the physician survey (n=42) experienced sensorineural deafness,[41] and we found no other publications that specifically describe an impact of CNS on auditory function. Visual system injury is a theoretical risk of repeated, high-intensity, retinal light exposure. However, the only study in which visual function was assessed revealed no difference relative to age-matched siblings in the visual acuity or color discrimination of 20 CNS-I patients whose eyes were unshielded for a mean of >40,000 hours of phototherapy.[32]

What is the course of disease progression in CNS and what are the factors associated with it?

In newborns with CNS-I, unconjugated bilirubin increases at a rate of 3–6 mg/dL per day[32] prior to the initiation of phototherapy, and typically peaks at pre-treatment values between 19.8±4.5 mg/dL and 20.5±5.5 mg/dL.[41] Despite consistent phototherapy exposure, patients

with CNS-I experience increasing bilirubin levels with advancing age; over 16 years of follow-up, Strauss et al. reported a mean increase in total bilirubin of 0.8 mg/dL per year in CNS-I patients receiving phototherapy since the age of 6±5 days.[32]

Liver fibrosis appears to develop in a proportion of CNS-I patients over time, as suggested by Mitchell et al.,[29] who found pericentral, periportal, and mixed patterns of fibrosis in 9 (41%) of 22 CNS-I explants at the time of transplant, and noted that patients with fibrosis were older (16.1 years) than those without (10.5 years; p=0.02).

Transient exacerbations of hyperbilirubinemia have been reported in response to respiratory infections, febrile illnesses, vaccinations, fasting, surgeries, emotional stress, and nonadherence with phototherapy. In one study, 10 (50%) of 20 CNS patients required cholecystectomy to manage worsening hyperbilirubinemia associated with cholelithiasis.[32] A diverse range of medications that compete with bilirubin for a single, high-affinity albumin binding site have been linked with an increased risk of kernicterus.[32,41]

What mortality has been reported in CNS and what are the factors associated with it?

Before the advent of phototherapy and liver transplantation, CNS-I was invariably fatal, with death typically occurring within the first 2 years of life.[1,7,8] Phototherapy and liver transplantation have dramatically decreased mortality attributable to CNS. Strauss et al.[32] reported 100% survival among 20 CNS patients (four [20%] with liver transplantation) followed over 16 years and van der Veere et al reported 91% survival among 57 CNS patients (21 [37%] with liver transplantation) over 28 years.[7] Rates of mortality following liver transplantation are discussed under the liver transplantation section below.

What is the standard of care treatment of CNS and what is its related burden?

Exchange transfusion

Exchange transfusion is sometimes used for emergent management of CNS during the neonatal period. This approach is effective at rapidly lowering serum bilirubin concentrations,[2,3,8] but has been associated with considerable complications, including thrombocytopenia, portal vein thrombosis, necrotizing enterocolitis, and sepsis.[3]

Phototherapy

Phototherapy has changed the natural history of CNS, allowing prolonged survival without neurologic deficits,[2,5,8] and is the foundation of treatment for all CNS-I and some CNS-II patients.[3] In the absence of liver transplantation, however, phototherapy is considered by many to be the greatest burden of CNS, requiring whole-body exposure for up to 10 to 12 h/day.[5] The large majority of CNS patients receive phototherapy overnight, and evidence suggests that this does not interfere with rhythmic melatonin production, and therefore circadian rhythms.[25] However, lifelong reliance on such systems causes considerable inconvenience and significant lifestyle constraints[8,32] including restricted travel and social opportunities. Other limitations include difficulties in temperature maintenance and the need for near nakedness during phototherapy.[7,8,41] While blue fluorescent tubes conventionally used for phototherapy tend to be large, heavy, and expensive, and require a dedicated power source, the increasing availability of light emitting diode (LED) sources goes some way to ameliorating this burden.[42,43]

Phototherapy appears less effective with advancing age for a number of reasons including increasing skin thickness, increasing body surface to weight ratio, and restricted hepatobiliary clearance of lumirubin.[8,29,32] This waning efficacy inevitably increases the risk of neurological injury[3,8,23] and is a major reason why adolescent and adult CNS-I patients usually require liver transplantation. Phototherapy is also associated with a number of side effects of different degrees of severity, including hyperkeratosis (thickening of the skin), skin rashes, and bullous excoriation, diarrhea and dehydration.[7,43,44]

Although phototherapy lamps (particularly the older-style fluorescent phototherapy tubes) can be costly to purchase, use, and maintain,[7,8,41] we found no formal cost analyses in the published literature.

Pharmacological treatment

The principal pharmacological categories used to treat patients with CNS include enzyme-inducing agents (phenobarbital), bilirubin-binding agents (calcium phosphate and orlistat), choleretics (ursodiol), and heme-oxygenase inhibitors (tin-protoporphyrin and zinc-protoporphyrin), with many adjunctive therapies also reported.[2,3,8,36,41] The evidence for the efficacy of any of these approaches is limited. Phenobarbital has some efficacy in patients with CN-II, and can be used to distinguish between CNS-I and CNS-II.[3] Small (n=11–16),

randomized, cross-over clinical trials have shown an increase in fecal unconjugated bilirubin excretion with orlistat[3,39] and a significant reduction in bilirubin levels for calcium phosphate;[3,40]; however, few outcomes data are provided.

As is the case for many rare disorders, there is wide inter- and intra-individual variation in the pharmacological management of CNS, and thus we could draw few conclusions about the relative efficacy and safety of individual agents. However, one RCT reported more gastrointestinal side effects among CNS patients receiving orlistat versus placebo,[39] whereas a second RCT for CNS reported no increase in adverse events for oral calcium phosphate versus placebo.[40] Tin-protoporphyrin (zinc-mesoporphyrin), which transiently decreases the production of native Z,Z-bilirubin, is thought to increase skin photosensitivity and may lead to iron-deficient anemia.[3]

Liver transplantation

Two principal types of liver transplantation are used to treat patients with CNS: orthotopic liver transplantation (OLT) and auxiliary partial orthotopic transplantation (APOLT). In OLT, the entire host liver is replaced with a whole or partial liver graft from a living or deceased allogeneic donor. In APOLT, only part of the native liver is removed and replaced with a donated liver segment.[8] Sze et al.[33] showed that graft survival was similar between APOLT and OLT (93% vs. 100%, 70% vs. 100%, and 70 vs. 75% at 1, 5, and 7 years, respectively; p=0.12), as was patient survival (100% vs. 100%, 90% vs. 100%, and 90% vs. 75% at 1, 5, and 7 years, respectively; p=0.87).[33]

The published data suggest that OLT remains more common than APOLT,[6,41] but the latter leaves open the option for future therapies directed at native hepatocytes (e.g. gene replacement and genome editing).

In studies comprising patients transplanted for various metabolic disorders, of which CNS represented only a small proportion,[7,26–28,32–35,37–39] post-transplant survival rates were 86–100% at 1 year, 81–95% at 5 years, and 79–92% at 10 years (Table 3), and predictors of mortality were impaired physical growth,[37] black race,[28] mismatched graft-to-recipient weight ratio,[37] older recipient age,[35] mismatched blood group and, [35] re-transplantation.[35]

General burdens of transplantation in CNS-I include the invasive and costly nature of the procedure, limited availability of suitable donors, and a variety of well established post-transplant medical and surgical morbidities.[41] Graft failure and adverse effects of immunosuppression (e.g. sepsis and malignancy) may occur after liver transplantation.[3] Liver transplantation does not reverse or alleviate pre-existing neurological damage.[7]

Between 14% and 67% of CNS patients report one or more significant complications related to OLT (Table 4).[19,23,31,32,41] Complications specific to this approach include bile duct obstruction, small bowel obstruction, and pleural effusion. Data from two publications suggest that 40–83% of CNS patients experience complications of APOLT (Table 4).[21,41] Graft atrophy occurs in a significant proportion of patients after APOLT; this may result from poor portal venous inflow, impaired hepatic venous outflow, or a lack of hepatotrophic substances.[21]

Liver segments from living donors are potentially suitable where there is a severe shortage of deceased donor organs or within societies that view deceased donor transplantation as culturally unacceptable (Table 4).[18,20] Leakage at the bile duct anastomosis was reported as a specific complication following a living donor transplant for CNS.[20]

Hepatocyte transplantation, in which between 5% and 15% of the host liver is replaced with transplanted hepatocytes,[45,46] and gene therapy, including injections of naked plasmid DNA and the use of AAV vectors,[47] are currently being investigated as potential therapies for CNS. These approaches show some promise in pre-clinical models,[48–51] but to date, liver transplantation remains the only curative therapy for CNS-I. Investigational AAV8 gene therapy products containing the *UGT1A1* gene are currently undergoing investigation in clinical trials.[52,53]

DISCUSSION

Overview

In this literature review, we compiled findings from 28 publications in an effort to systematically describe the disease burden associated with CNS. Except for isolated anecdotal comments about the practical challenges of daily phototherapy, we found no specific data about the humanistic or economic burdens of CNS. Thus, our findings focus principally on its clinical aspects.

The primary clinical feature of CNS is elevated unconjugated bilirubin levels. The published data show considerable variability in serum bilirubin levels among CNS-I patients and the rate of bilirubin-induced brain injury ranges between 0% and 42%. In newborns with CNS-I, the inexorable increase of bilirubin will almost inevitably cause kernicterus without the institution of high quality phototherapy before 14 days of age. Even with appropriate management, hyperbilirubinemia progressively increases throughout childhood, and may be subject to episodic and dangerous exacerbations as a result of common infections, surgeries, biliary stasis, emotional stress, and phototherapy system malfunction or nonadherence. Drug-albumin interactions, which can go unrecognized in certain clinical settings, pose a continual threat to CNS patients.

The only published data specific to CNS-I report overall mortality ranging from 0% (16-year follow-up)[32] to 9% (28-year follow-up).[7] Once a CNS patient receives a liver transplant, the latter takes over as the main determinant of morbidity and untimely death. Studies of liver transplantation that comprise patients with a range of metabolic disorders (including a small proportion of CNS) report 1-, 5-, and 10-year survival rates of 87–100%, 81–95%, and 79–92%, respectively.[26–28,33–35,37,38] However, such studies do not report survival by specific indication, and therefore do not allow for conclusions particular to CNS. Our collective professional experience suggests that post-transplant survival among CNS patients is higher than broader population rates. For example, the Scientific Registry of Transplant Recipients (SRTR) database includes 67 CNS patients (predominantly CNS-I) who underwent their first liver transplant at a mean age of 9.3 years and had 1-, 5-, and 10-year survival rates of 98.5%, 96.1%, and 96.1%, respectively. Kaplan-Meier analysis revealed mean post-transplant survival time of almost 22.5±1.7 years. Clinical records of 26 CNS-I patients managed at King's College Hospital, London, indicate 1-, 5-, and 10-year post-transplant survival rates of 100%, 96% and 96%, respectively, and survival was 100% among 19 patients with CNS-II, only a minority of whom had liver transplants.

No publications report general risk factors for mortality in CNS, although some data are predictive of mortality post-transplant. For example, impaired physical growth at time of transplant was linked to higher post-transplant mortality in one study,[37] but this fact likely reflects differences in the underlying disease process rather than the transplant procedure itself. For reasons that are not clear, black patients appear to have higher post-transplant mortality.[28]

Among all treatment modalities for CNS, phototherapy appears to represent the greatest burden to patients. Daily phototherapy is costly, imposes significant practical and social constraints, and shows waning efficacy with advancing age. Two recent focus group meetings with families affected by CNS (Audentes Therapeutics, data on file) revealed that caregivers also experience considerable financial, psychological, and emotional hardship as a result of phototherapy. The safe operation of large, powerful light systems restricts travel not only for the patient, but also other family members. Caregivers find it difficult to maintain consistent phototherapy across the arc of youth; infants often need swaddling and wake frequently during the night, older children may develop anxiety about their lights, and strict adherence is difficult to enforce in teenagers. Several patients and their caregivers reported considerably compromised sleep. Not surprisingly, parents worry about the emotional impact of jaundice and phototherapy on their children, who are unable to participate in certain social events, may feel stigmatized by their appearance and, as they grow older, could face important limitations in social interactions.

These factors, combined with the ever-present fear of kernicterus, were cited as the reasons why many families elect liver transplantation, which is the only curative therapy for CNS-I and is associated with high post-transplant survival in this population. However, liver transplant in CNS-I is not without its challenges, including high cost, limited availability of donors, the potential for graft failure or atrophy, and a host of complications that can arise from chronic immunosuppression.[3] Interestingly, focus group discussions revealed that the parents of some children who had received a liver transplantation nevertheless experienced ongoing anxiety about the possibility of graft failure, even though the actual risk of this complication diminishes considerably over time. It appears that OLT remains the preferred transplantation technique but, unlike APOLT, does not leave open the option for future gene or cell-based therapies. Clinical research in this area is underway, with gene therapy clinical studies ongoing.[52,53]

Gaps and limitations

As can be expected for any ultra-rare disorder such as CNS, there remain significant gaps in our understanding about its clinical presentation, management, and progression before and after liver transplantation. Specifically, few data address CNS-attributable mortality or its determinants, and there are limited about re-transplantation rates. Only limited data address major comorbidities of CNS, although some describe the adverse effects of available

treatments (e.g. dermatologic complications of phototherapy). As such, the clinical evidence base used for managing CNS is largely limited to relatively small case series and retrospective cohorts, with sample sizes ranging from two to 57 individuals. The most conspicuous gap revealed by our review is the absence of humanistic and economic data about CNS; this should prompt future studies that specifically explore the impact of this rare condition on quality of life, daily functioning, and both direct and indirect costs to patients, families, healthcare systems, and society.

Future perspectives

In conclusion, CNS is associated with a substantial burden for patients, even with existing standards of care such as phototherapy or liver transplantation. Although liver transplantation is considered definitive treatment, it is not without significant risks and complications. Future models of care for liver-based monogenic disorders could be based on cellular or genetic platforms. Although hepatocyte cell transplantation has shown some transient efficacy in humans, broader implementation into clinical practice has been hampered by several procedural and practical limitations. Identifying an ample source of hepatocytes for transplant remains challenging, as does optimizing cell quality and storage. Furthermore, hepatocyte transplant currently suffers from incomplete efficiency of cellular transfer, the inability to effectively monitor cellular graft function and rejection often resulting in post-infusion demise of transplanted cells, and the need for protracted immunosuppression.[54,55] *Ex vivo* gene therapy of autologous liver or induced pluripotent stem cells and their subsequent infusion into the native liver may be possible, but current safety and efficacy data are limited. Less invasive and cumbersome technologies, such as *in vivo* gene replacement using AAV8 or a comparable vector delivery system,[55,56] hold considerable promise and are currently being studied in humans.[52] Indeed, liver-targeted AAV gene therapy has been shown to be safe and effective for hemophilia B, with patients monitored for up to 6 years so far.[58–60] If equally successful, gene therapies may decisively improve the lives of CNS patients and their families.

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Table 1. Basic characteristics of publications reporting on clinical burden of CNS

Publication (Quality rating)	Study design	Population (sample size); age at start of study	Study objective	Outcome measurement	Summary of results
Adam et al. 2012[35] (5/9)	Retrospective cohort (Europe)	CNS (type not specified; n=59); NA	To investigate the evolution of indications and results of liver transplantation in Europe	Indications for LT, mortality for LT, patient survival, living-related LT, re-LT	1) From 1988–2009, 1-, 5-, 10-, and 15-year graft/patient survival rates in CNS were 88/97%, 79/92%, 79/92%, 79/92%, respectively 2) From 1999–2009, 1- and 5-year graft/patient survival rates in CNS were 86/100%, 76/95%, respectively
Al Shurafa et al. 2002[18] (5/9)	Case series (Saudi Arabia)	CNS-I (n=6); 1 year 2 months–12 years	To analyze the outcome of children with CNS-I and report the first 3 LDLTs for CNS-I in Saudi Arabia/Middle East	Postoperative bilirubin levels; requirement for phototherapy post-transplant; complications post-transplant	Postoperative bilirubin levels returned to normal in all 3 transplanted children; no further phototherapy was required
Al-Shurafa et al. 2001[8] (NA)	Review (International)	CNS-I and CNS-II (n=NA); NA	To describe the management of CNS-I	NA	1) Ideal age for transplantation is 3–5 years 2) OLT is believed to be the preferred method of liver transplantation for CNS-I
Arnon et al. 2010[26] (6/9)	Retrospective cohort (US)	Pediatric recipients of liver allograft for metabolic diseases, including CNS[†] (n=446; CNS=21); 0–17 years	To assess post-liver transplant outcomes and risk factors for mortality and graft loss in children with metabolic disorders vs. non-metabolic diagnoses	Patient survival, graft survival, rejection, growth, immunosuppression	1) 1- and 5-year patient survival was significantly greater in children with metabolic diseases vs. other diseases (94.6% and 88.9%, vs. 90.7% and 86.1%, respectively; p=0.05) 2) 1- and 5-year graft survival was significantly greater in children with metabolic

					diseases vs. other diseases (90.8% and 83.8% vs. 85.4% and 78.0%, respectively; p=0.005) 3) Children with metabolic diseases were less likely to experience GI complications, PVT and reoperations within 30 days post-transplant vs. other indications
Fernandes et al. 2016[24] (NA)	Case report (Portugal)	CNS-II (n=1); 80 years	To describe a case of acute cholangitis in a patient with CNS type II	NA	1) Second report of cholangitis in a patient with CNS 2) Pigmented gallstones may follow in the long-term in mild CNS
Fitzpatrick et al. 2008[3] (NA)	Review (International)	CNS-I and CNS-II (n=NA); NA	To describe the therapeutic options and consequences of mutations in the UGT1A1 complex in CNS	NA	Review of emerging gene therapies for CNS-I
Gridelli et al. 1997[19] (3/9)	Case series (Italy)	CNS-I (n=5); not stated	To report experience with OLT in five children with CNS	EEG; BMR; AEP; SPECT; Bilirubin; Surgical complications; AST/ALT; BUN/creatinine levels	Following OLT, all patients were alive and well, and 4/5 were in the school grade appropriate to age
Haberal et al. 2016[27] (6/9)	Retrospective cohort (Turkey)	Pediatric recipients of liver transplant, including 'other'‡ (n=215; Other=43); 0.2–18 years	To evaluate pediatric liver transplantation in terms of outcomes, complications, and long-term follow-up results	Post-transplant complications, mortality, 5- and 10-year survival rate	1) Post-transplant biliary complications were biliary leakage (16.2%) and biliary stricture (14.8 %) 2) Complication rates in hepatic artery and portal vein were 16.7% and 4.6%. Overall mortality rate was 17.8% (82.3% at 5 years; 78.9% at 10 years)

Hafkamp et al. 2007[39] (Unclear risk of bias)	RCT (The Netherlands)	CNS-I and CNS-II (CNS-I: n=7; CNS-II: n=9); 8–51 years	To determine the effects of orlistat on plasma unconjugated bilirubin concentrations in CNS patients	General effects of orlistat; plasma UCB concentration; fecal fat and UCB excretion; characteristics of responsive vs. non-responsive patients; Side effects and compliance	1) Orlistat increased fecal fat excretion (+333%) and fecal UCB excretion (+43%) vs placebo, and significantly decreased plasma UCB concentration (–9%) 2) In 7/16 patients, the decrease in plasma UCB levels was clinically relevant (>10%, mean 21%), and negatively correlated with fecal fat excretion (r=– 0.93) 3) Clinically relevant response to orlistat treatment appeared correlated with lower dietary fat intake
Jansen et al. 1999[2] (NA)	Review and survey (International)	CNS-I and CNS-II (CNS-I: n=15)	To describe the diagnosis and management of CNS	NA	1) Patients with brain damage at transplantation were significantly older than those with no brain damage (14.3 vs. 5.9 years; p=NR)
Kayler et al. 2003[28] (6/9)	Retrospective cohort (US)	Children with a primary diagnosis of metabolic disease including CNS-I (n=2,728; CNS: n=12); age 5 months–18 years	1) To investigate survival advantage in a large cohort pediatric liver transplantation patients	Survival	1) Adjusted 1- and 5-year survival rates were significantly higher in children with metabolic disease vs biliary atresia (94% and 92% vs. 90% and 86%, respectively; p=0.008) 2) Outcomes were significantly better in metabolic disease than biliary atresia
Kummer et al. 2016[36] (NA)	Prospective cohort (Switzerland)	CNS-II (n=1); not stated	To monitor total serum bilirubin concentration in a CNS-II patient treated with hypericum extract	NA	Hypericum reduced midazolam exposure by 42% and total serum bilirubin concentration by 30–35%

Mazariegos et al. 2014[34] (5/9)	Retrospective single-center cohort (US)	Children with primary diagnosis of metabolic disease including CNS-I (n=285; CNS-I n=15); not stated	To describe 30 years of outcome data regarding pediatric liver transplantation for metabolic diseases	Survival, graft survival	1) Patient and graft survival in the CNS-1 cohort was 100% 2) Over the last 15 years, significant improvement in patient and graft survival was demonstrated, with a sharp reduction in early death or graft loss, and maintenance of patient and graft survival over >15 years 3) Survival rate is 97% among patients receiving transplants over the past decade at CHP
Mitchell et al. 2017[29] (6/9)	Retrospective cohort (US)	CNS-I (n=22); 13.4 (5.6) years	To investigate association between hepatic histology and disease phenotype in CNS-I explants	Rates of fibrosis, liver dysfunction, portal hypertension	1) Nine (41%) explants had significant fibrosis 2) Mean age of subjects with fibrotic versus was significantly greater vs. non-fibrotic livers (16.1 vs. 10.5 years; p=0.02)
Morioka et al. 2005[37] (5/9)	Prospective cohort (Japan)	Patients with inheritable metabolic disorders including CNS-I (n=46; CNS-I: n=2); not stated	To determine outcomes of LDLT, factors for post-transplant patient survival and the impact of heterozygous donors	Post-transplant survival; Recovery in growth retardation; Postoperative complications	1) 1- and 5-year post-transplant cumulative patient survival rates were 86.8% and 81.2%, respectively 2) Post-transplant cumulative patient survival rates were significantly higher in LOD vs. NLOD and in patients with normal/slightly delayed physical growth vs. patients with delayed physical growth at time of LDLT 3) Earlier age of onset or longer time from onset to LDLT was associated with worse retardation of growth

Morioka et al. 2005[38] (5/9)	Prospective cohort (Japan)	Patients with NCIMLD, including CNS-I (n=21; CNS-I: n=2); 4 months–58 years	To evaluate the outcome of LDLT for NCIMLD to clarify the effects of using a heterozygous donor	Survival; Neurologic impairment; Physical growth retardation	1) 1- and 5-year cumulative survival rate was 85.7% 2) At follow-up, all surviving recipients were well with no sequelae 3) No mortality or morbidity related to use of heterozygous donors was seen in donors or recipients
Nazer et al. 1998[30] (4/9)	Retrospective cohort (Saudi Arabia)	CNS-I (n=12); not stated	To report experience with CNS in a tertiary care center in an area with a high rate of consanguineous marriage	Response to treatment; Liver biopsy; UGT1A1 activity	1) Jaundice was detected in the first few days of life in 11/12 patients (detection was delayed for 2 weeks in 1 patient, resulting in kernicterus 2) No patients responded to phenobarbital therapy alone (6 patients required phenobarbital /phototherapy; 6 patients required phototherapy alone) 3) Percutaneous liver biopsy led to minimal and focal cholestasis in 8/10 patients 4) Near complete absence of UGT1A1 activity in the liver (0.005–0.02 nmol/min/mg protein) was reported in 7 cases 5) Kernicterus developed in 5 cases

Özçay et al. 2009[20] (5/9)	Case series (Turkey)	CNS-I (n=4); 2 months–13 years	To assess the effectiveness of LDLT in CNS-I	Survival; Neurodevelopmental milestones	1) Unconjugated bilirubin concentration normalized at D1 after OLT 2) In 2 patients, bile leakage developed at the anastomosis (treated with repeated cholangioplasty) 3) 1-week post-OLT, a 2-month-old infant with suspected bilirubin encephalopathy exhibited hypotonia, spasticity, and lack of head control. He died after vomitus aspiration at 10 months post-OLT 4) At follow-up, 3 patients were alive with normal neurodevelopmental milestones
Pett et al. 1987[31] (3/9)	Retrospective cohort (UK)	Patients with persistent, nonhemolytic hyperbilirubinemia, including CNS (CNS-I: n=7; CNS-II: n=5); 4 months–10 years	To report clinical experience in 12 CNS cases and emphasize the variability of the two types of disorder	Serum bilirubin; psychometric assessment; clinical assessment	1) In all CNS-I children, serum bilirubin concentration decreased significantly with phototherapy (40–80%), but increased gradually in every case as the child aged; 6/7 children showed normal developmental progress and no neurologic abnormalities 2) In CNS-II, serum bilirubin concentrations during phenobarbital therapy fell by 33–77%; no patients had developmental delay or neurologic abnormalities
Rela et al. 1999[21] (5/9)	Case series (UK)	CNS-I (n=6); 8–18 years	To determine if APOLT has the long-term potential to correct the underlying abnormality in CNS-I without the need for	Bilirubin levels; Acute rejection	1) Median serum bilirubin level was 50 µmol/L on D5 after transplant, decreasing to 23 µmol/L at 32 months (median follow-up) 2) Early severe acute rejection developed in 4

			total liver replacement		children requiring conversion to tacrolimus (1 patient died from lymphoproliferative disease 6 months after a second transplant)
Rubboli et al. 1997[22] (5/9)	Case series (Italy)	CNS-I (n=5); 4–20 years	To study neurophysiological features of patients with CNS-I	Neurophysiological features (multimodal evoked potentials and periodic EEG polygraphy recordings); brain CT and MRI scans	1) 2 patients presented with late onset neurologic disturbances 2) EEG abnormalities were observed in 3 patients 3) Remarkable improvement in EEG activity was observed in 1 patient with neurologic impairment after liver transplantation
Schauer et al. 2003[23] (4/9)	Case series (Germany)	CNS-I (n=3); 4–12 years	To report experience with OLT in 3 CNS-I patients undergoing early LT	Surgical complications; neurological complications	1) OLT was uneventful in all recipients 2) One symptomatic patient (7 years) completely recovered from neurologic deficits 36 months after OLT; a second (12 years) had significantly improved symptoms at 27 months 3) All patients attended school at appropriate grades at the end of follow-up
Stebelova et al. 2017[25] (5/9)	Case report (Slovak Republic)	CNS-I (n=1); 9 years	To investigate whether intense blue light phototherapy for severe hyperbilirubinemia suppresses melatonin production at night (with use of a sleep mask)	6-sulphatoxymelatonin urine concentration	1) A distinct melatonin production rhythm was found; patient 6-sulphatoxymelatonin urine concentration was comparable with the control group 2) No differences in 6-sulphatoxymelatonin levels were found between phototherapy vs. no phototherapy at night

Strauss et al. 2006[32] (4/9)	Retrospective cohort plus case series (US)	CNS (CNS-I: n=19; CNS-II: n=1); age 0.8–21 years	To summarize the treatment of 20 CNS patients at 1 center (1989 to 2005)	Vision testing; Hospitalization rate; Neurologic outcomes	1) Mean total bilirubin increased with age by ~0.8 mg/dl/year 2) Non-surgical hospitalization rate was 0.12 hospitalizations/patient/year (50% for neonatal hyperbilirubinemia; 50% for infectious illnesses) 3) Visual acuity and color discrimination did not differ between CNS-I patients and age-matched sibling controls 4) 4 patients treated with OLT were effectively cured (1 suffered significant transplant-related complications)
Suresh et al. 1997[41] (2/9)	Cross-sectional (US, Europe, Australia, Saudi Arabia)	CNS-I (n=42); 2 months–21 years	To determine the current clinical status of patients with CNS and therapies being used	Height/weight; Developmental status; Kernicterus; Cerebellar symptoms; Hearing status	1) All 42 patients were of normal height and weight; neurodevelopmental status was normal in 77% of patients 2) 2 patients had kernicterus, 4 had cerebellar symptoms, and 1 each had developmental delay, mild intention tremor, and mild speech delay 3) Hearing was normal in 94% of patients
Sze et al. 2009[33] (4/9)	Retrospective cohort (UK)	CNS-I (n=11); not stated	To report a single-center experience of pediatric liver transplantation for liver-based metabolic disorders and to compare the outcome of cirrhotic versus noncirrhotic	Patient survival, graft survival, graft function, complication rate, and Growth	1) Cumulative 1-, 5-, and 10-year graft and patient survival rates were 83%, 77%, and 62% and 91%, 86%, and 82%, respectively 2) Acute liver failure at first presentation (HR 3.0; 95% CI 1.1–8.1), age <1 year at transplantation (HR 4.6; 95% CI 1.7–12.4) and

			metabolic liver disease		hospitalization (HR 3.2; 95% CI 1.1–9.3) were significant predictors of worse patient survival 3) For noncirrhotic disorders, the long-term patient (100% vs. 100%, 90% vs. 100%, and 90% vs. 75%, p=0.87) and graft survival rates (93% vs. 100%, 70% vs. 100%, and 70 vs. 75%, p=0.12) at 1, 5, and 7 years for auxiliary versus orthotopic transplantation were not significantly different
van der Veere et al. 1996[7] (5/9)	Cross-sectional (US, UK, Germany, Netherlands, France, Canada, Australia, Austria, Belgium)	CNS-I (n=57); 1–18 years	To find guiding principles for physicians in the care of patients with CNS-I	Brain damage; kernicterus	1) Brain damage developed in 15 patients (26%) 2) 5 patients died; 10 experienced some mental or physical handicap 3) In 2 patients, early signs of bilirubin encephalopathy were reversed with prompt medical intervention/liver transplantation (n=1) and prompt liver transplantation (n=1) 4) 7 patients had some brain damage at time of transplantation; 1 died after re-transplantation, 2 improved neurologically, 4 remained neurologically impaired 5) Younger age protected against brain damage
Van der Veere et al. 1997[40] Unclear risk	RCT (The Netherlands)	CNS-I and CNS-II (n=CNS-I: n=5; CNS-II: n=6); 2–42 years	To evaluate the effect of oral calcium phosphate supplementation on plasma	Serum bilirubin levels; Urinary calcium and phosphate output	1) A modest but significant decrease in serum bilirubin was seen in CNS-I (18±6%, p=0.03)

of bias	bilirubin levels in CNS patients	but not CNS-II patients during calcium phosphate treatment 2) Urinary calcium and phosphate output did not change during the treatment period

AEP=Auditory evoked potentials; ALT=Alanine transaminase; APOLT=Auxiliary partial orthotopic transplantation; AST=Aspartate transaminase; BMI=Body mass index; BMR=Brain magnetic resonance; BUN=Blood urea nitrogen; CHP=Children's Hospital of Pittsburgh; CI=Confidence interval; CNS=Crigler–Najjar syndrome; CT=Computed tomography; D=Day; EEG=Electroencephalography; GI=Gastrointestinal; HR=Hazard ratio; ICU=Intensive care unit; LDLT=Living donor liver transplantation; LOD=Liver-oriented disease; LT=Liver transplant; MRI=Magnetic resonance imaging; NA=Not applicable; NCIMLD=Noncirrhotic inheritable metabolic liver disease; NLOD=Non-liver-oriented disease; NR=Not reported; OLT=Orthotopic liver transplantation; PVT=Portal vein thrombosis; RCT=Randomized controlled trial; SPECT=Single photon emission computed tomography; UCB=Unconjugated bilirubin; UK=United Kingdom; US=United States

†CNS not specified as CNS-I or CNS-II

‡'Other'=Alagille syndrome, alpha1-antitripsin deficiency, Crigler–Najjar syndrome, glucose-6-phosphate dehydrogenase deficiency, hypercholesterolemia, hemophagocytic syndrome, and hyperoxalosis

Quality rating refers to a quality score assigned to each publication considering characteristics that could introduce bias, using the following tools: 1) Newcastle-Ottawa Scale for cohort studies and case-control studies;[15] 2) Adapted Newcastle-Ottawa Scale for cross-sectional studies;[15] 3) AMSTAR measurement tool for reviews;[16] 4) Cochrane risk of bias assessment tool for randomized controlled trials[17]

Table 2. Summary of complications of kernicterus in CNS patients reported in case series

Study	Description	Reported complications of kernicterus
Gridelli et al. 1997[19]	Five CNS-I pediatric patients (Italy)	Episodes of kernicterus prior to liver transplantation, ataxic movement, near inability to walk or talk (all exhibited in one patient)
Schauer et al. 2003[23]	Three CNS-I pediatric patients (Germany)	Intellectual disability, physical retardation, and episodes of apathy as well as a slurred speech (two patients)
Rubboli et al. 1997[22]	Five CNS-I pediatric patients (Italy)	Neurological impairment, with symptoms ranging from mild motor impairment, difficulties in writing, diffuse hypotonia, myoclonic jerks, convulsive seizures, mental slowing, ataxia, modifications of mood and behavior, progressive sleepiness and apathy, and impaired consciousness (two patients)
Pett et al. 1987[31]	Seven CNS-I pediatric patients in UK	Delayed language development (one patient); intellectual disability reported (one patient)
Rela et al. 1999[21]	Six CNS-I pediatric patients in UK	Long tract neurologic signs presenting with mild weakness in both legs prior to transplantation (one patient)
Nazer et al. 1998[30]	12 pediatric patients with CNS-I in Saudi Arabia	Kernicterus (five patients)

CNS=Crigler–Najjar syndrome

Table 3. Reported survival rates in CNS patients alone and liver transplant populations including CNS patients

Publication	Population	Patient survival			
		1-year	5-year	10-year	Other
CNS only					
Strauss et al. 2006[32]	CNS-I (n=19); CNS-II (n=1)	–	–	–	100% (16 years)
van der Veere et al. 1996[7]	CNS-I (n=57)	–	–	–	91% (28 years)
Adam et al. 2012[35]	CNS (NS; n=59): 1988–2009	97%	92%	92%	92% (15 years)
	1999–2009	100%	95%	–	–
Mixed populations					
Arnon et al. 2010[26]	Pediatric recipients of liver allograft for metabolic diseases, including CNS† (n=446; CNS=21)	94.6%	88.9%	–	–
Haberal et al. 2016[27]	Pediatric recipients of liver transplant, including 'other'‡ (n=215; Other=43)	–	82.3%	78.9%	–
Kayler et al. 2003[28]	Children with a primary diagnosis of metabolic disease including CNS-I (n=551; CNS-I: n=12)	94%	92%	–	–
Mazariegos et al. 2014[34]	Pediatric recipients of liver transplant, including CNS-I (n=285; CNS-I: n=15)	87.7%	84.9%	80.1%	70.1% (20 years)
Morioka et al. 2005[37]	Patients with inheritable metabolic disorders including CNS-I (n=46; CNS-I: n=2)	86.9%	81.2%	81.2%	–
Morioka et al. 2005[38]	Patients with NCIMLD, including CNS-I (n=21; CNS-I: n=2)	85.7%	85.7%	–	–
Sze et al. 2009[33]	Children with a primary diagnosis of metabolic disease including CNS-I (n=96; CNS-I: n=11)	91%	86%	82%	–

CNS= Crigler–Najjar syndrome; NCIMLD=Noncirrhotic inheritable metabolic liver disease

†CNS not specified as CNS-I or CNS-II

‡'Other'=Alagille syndrome, alpha1-antitripsin deficiency, CNS syndrome, glucose-6-phosphate dehydrogenase deficiency, hypercholesterolemia, hemophagocytic syndrome, and hyperoxalosis. Number of CNS patients is not stated

Table 4. Complications of liver transplantation reported in included CNS publications

Publication	Population (n)	n with complications (%)	Complications
OLT			
Gridelli et al. 1997[19]	CNS-I (5 [all OLT])	1/5 (20%)	• Pleural effusion
Pett et al. 1987[31]	CNS-I (12 [7 OLT])	1/7 (14%)	• Bile duct obstruction and rejection; death
Schauer et al. 2003[23]	CNS-I (3 [all OLT])	2/3 (67%)	• 1 patient: acute rejection episodes; pleural effusion • 1 patient: acute rejection episodes; small bowel obstruction
Strauss et al. 2006[32]	CNS-I (20 [4 OLT])	1/4 (25%)	• 1 patient : Viral infectious complications with cytomegalovirus hepatitis and Epstein-Barr viremia, acute allograft rejection, and successfully treated post-transplant lymphoproliferative disease
Suresh et al. 1997[41]	CNS-I (42 [10 OLT])	2/10 (20%)	• 1 patient: repeat transplant • 1 patient: chronic mild hyperbilirubinemia
APOLT			
Suresh et al. 1997[41]	CNS-I (42 [5 APOLT])	2/5 (40%)	• 1 patient: graft atrophy; underwent OLT • 1 patient: chronic rejection
Rela et al. 1999[21]	CNS-I (6 [all APOLT])	5/6 (83%)	• 4 patients: early severe acute rejection • 1 patient: second transplant for chronic rejection and graft atrophy; death from lymphoproliferative disease
OLT VS. APOLT NOT SPECIFIED			
Sze et al. 2009[32]	CNS-I (96; APOLT vs. OLT NS)	67/96 (70%) 31/96 (32%) 16/96 (17%) 13/96 (14%)	• Acute rejection • Infection • Biliary complications • Chronic rejection

		10/96 (10%) 9/96 (10%) 5/96 (5%) 4/96 (4%) 4/96 (4%) 4/96 (4%) 3/96 (3%) 3/96 (3%)	• HAT • De novo AIH • Bowel complications • Primary graft failure • PVT • PTLD • Postoperative bleeding • Portal hypertension
LDLT			
Al Shurafa et al. 2002[18]	CNS-I (6 [3 LDLT])	2/3 (67%)	• Acute hepatocellular rejection
Özçay et al. 2009[20]	CNS-I (4 [all LDLT])	3/4 (75%)	• Bile leakage at the anastomosis in two patients • 1 patient with suspected bilirubin encephalopathy pre-transplant exhibited hypotonia, spasticity of the lower extremities, and lack of head control at 1-week post LDLT and died after vomitus aspiration during sleep at 10-months post LDLT

AIH=Autoimmune hepatitis; APOLT=Auxiliary partial orthotopic transplantation; CNS=Crigler–Najjar syndrome; HAT=Hepatic artery thrombosis; LDLT=Living donor liver transplantation; NS=Non-significant; OLT=Orthotopic liver transplantation; PTLD=Post-transplant lymphoproliferative disease; PVT=portal vein thrombosis

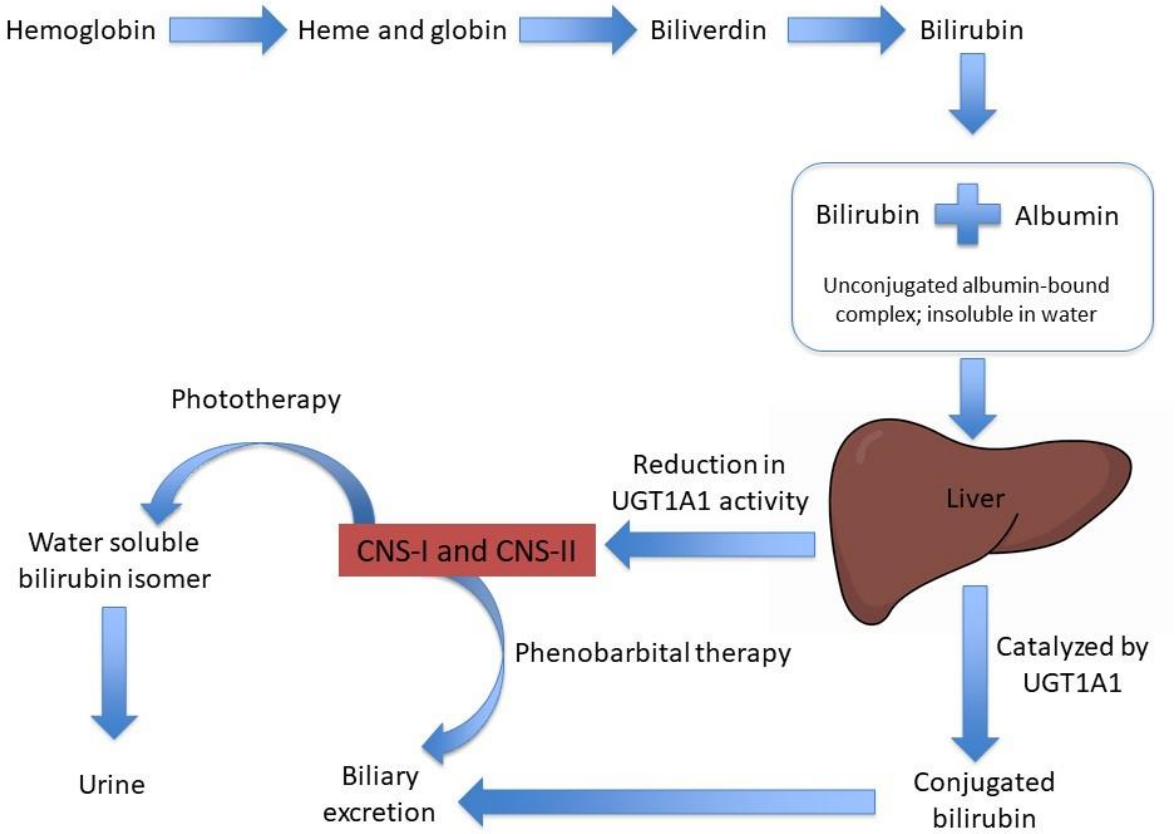

Figure 1. Schematic of bilirubin formation and excretion[2,3,61–63]

CNS=Crigler–Najjar syndrome

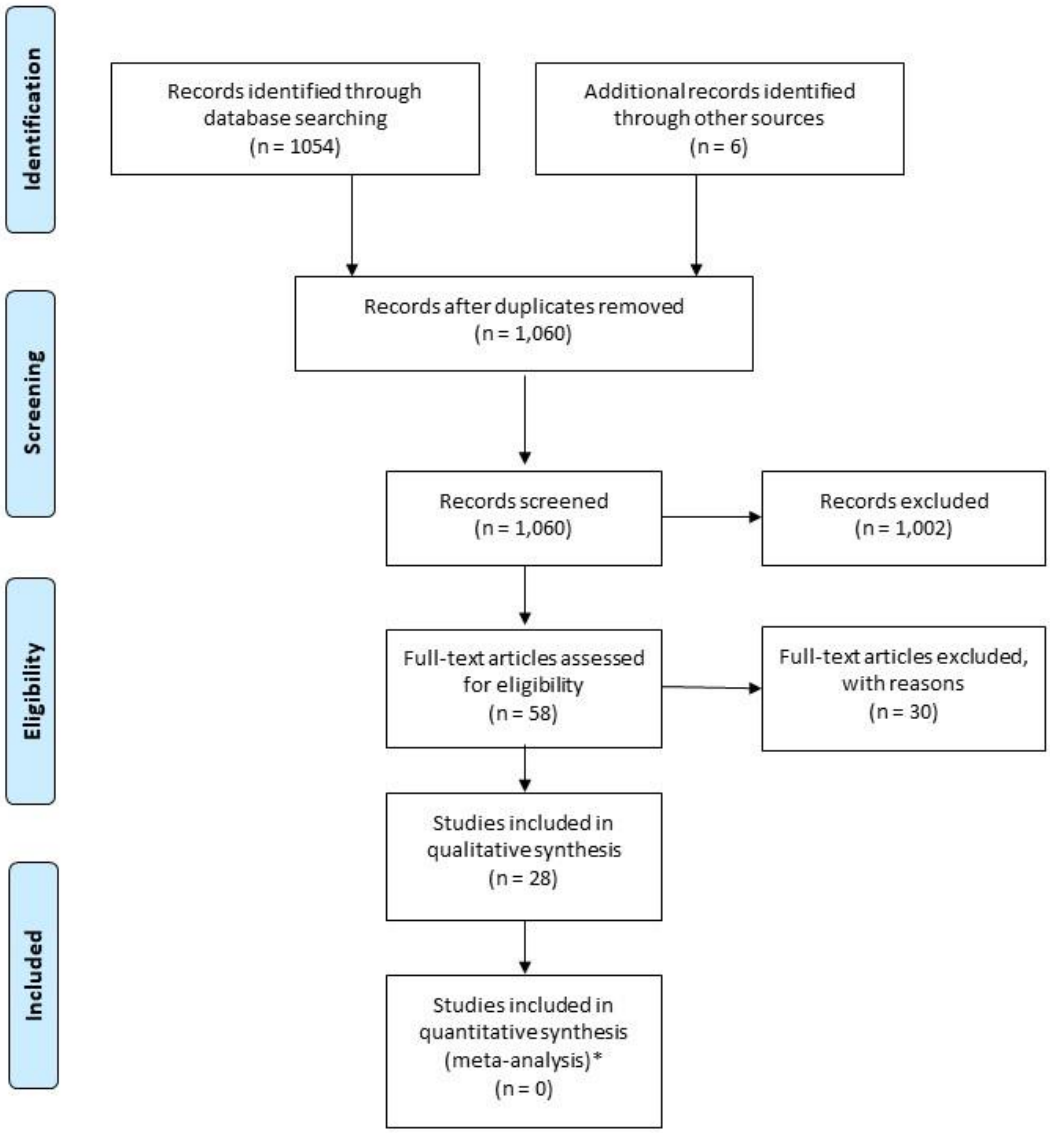

Figure 2. Flowchart of screening and identification process