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Neonatal cholestasis: recent insights

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Abstract

Background: Neonatal physiological jaundice is a common benign condition that rarely extends behind the second week of life; however, it may interfere with the diagnosis of a pathological condition termed neonatal cholestasis (NC). The latter is a critical, uncommon problem characterized by conjugated hyperbilirubinaemia. This review aims to highlight the differences between physiological and pathological jaundice, identify different causes of NC, and provide a recent approach to diagnosis and management of this serious condition.

Main text: NC affects 1/2500 live births, resulting in life-threatening complications due to associated hepatobiliary or metabolic abnormalities. NC is rarely benign and indicates the presence of severe underlying disease. If jaundice extends more than 14 days in full-term infants or 21 days in preterm infants, the serum bilirubin level fractionated into conjugated (direct) and unconjugated (indirect) bilirubin should be measured. A stepwise diagnostic approach starts with obtaining a complete history, and a physical examination which are valuable for the rapid diagnosis of the underlying disease. The most frequently diagnosed causes of NC are biliary atresia (BA) and idiopathic neonatal hepatitis (INH). The early diagnosis of NC ensures more accurate management and better prognosis. Despite the unavailability of any specific treatments for some causes of NC, the patient can benefit from nutritional management and early medical intervention. Future research should attempt to shed light on methods of screening for NC, especially for causes that can be effectively treated either through proper nutritional support, appropriate chemotherapeutic management, or timely surgical intervention.

Conclusion: Further attention should be paid for diagnosis and treatment of NC as it may be misdiagnosed as physiological jaundice; this may delay the proper management of the underlying diseases and aggravates its complications.

Keywords: Biliary atresia, Neonatal cholestasis, Management of jaundice, Physiological jaundice, Surgical causes of neonatal jaundice

Highlights

- Definition of neonatal cholestasis.
- Points of differentiation between physiological and pathological jaundice.
- Causes of neonatal cholestasis.
- Recent approach to diagnosis and management of neonatal cholestasis

Background

Neonatal physiological jaundice is a common benign condition that rarely extends behind the second week of life; unfortunately, it may delay the diagnosis of a pathological condition termed neonatal cholestasis (NC). The latter is a life-threatening, infrequent problem characterized by conjugated hyperbilirubinaemia. In many diseases associated with NC, multiple organs and body systems may be affected, and early intervention may significantly affect the outcome [1]. If jaundice extends more than 2 weeks in full-term infants or 3 weeks in preterm infants, the serum bilirubin level should be fractionated into conjugated and unconjugated bilirubin to exclude the diagnosis of NC [2].

In this review, I will highlight the main differences between physiological and pathological jaundice, identify different reasons of NC and provide a recent approach to diagnosis and management of many causes of NC.

NC is considered when the conjugated bilirubin level exceeds 1 mg/dL with a total bilirubin level ≤ 5 mg/dL or when the conjugated bilirubin is ≥ 20% of the total

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bilirubin that is > 5 mg/dL. It is crucial to detect and refer patients with NC to specialized medical centres to improve their management and prognosis [3].

Epidemiology

Globally, NC affects 1/2500 live births, and this incidence rate has remained steady from 1985 to 2017. Biliary atresia (BA) and idiopathic neonatal hepatitis (INH) are the most frequently diagnosed aetiologies [4].

Clinical presentation

Neonates may have immature bile acid excretion, resulting in a state of cholestasis [5]. This state may extend for the first 6 months of infancy, with increased vulnerability to other cholestatic agents. This fact makes NC is atypical feature of neonatal liver disease rather than a late manifestation [6]. NC is suspected when there is a prolongation of jaundice, necessitating further work-up for cholestasis [7]. Patients' complaints are usually related to fat-soluble vitamin insufficiency, i.e. prolonged prothrombin time. Clinical findings include related to the associated diseases, i.e. cardiac lesions in the case of Alagille syndrome.

Causes

Any factor that impedes the bile flow from the hepatocytes to the sphincter of Oddi results in a state of cholestasis [8]. NC can be due to either intra/extra-hepatic bile duct (IHBD/EHBD) obstruction or hepatocellular disease (defects in membrane transport, embryogenesis, or metabolic dysfunctions) [7]. Aetiologies of NC can be further divided into those that are surgically correctable and those that are not (Fig. 1).

Surgically correctable aetiologies

Biliary atresia

BA is the most common cause of liver transplantation (LT) in paediatric patients and needs urgent management to prevent liver cirrhosis. BA is a unique disease to the neonatal period representing the end result of a damaging inflammatory process with unclear aetiology affecting both intra- and extrahepatic bile ducts [9]. Incidence of BA varies worldwide ranging from about 1 in 5–10,000 live births in Japan, China and Taiwan to about 1 in 15–20,000 in Europe [10, 11]. Four different variants of BA can be distinguished based on clinical or laboratory features: isolated disease, cystic BA, virally associated BA especially with cytomegalovirus infection, and BA with splenic malformation syndrome. While the aetiology of BA is not fully understood with many interesting possibilities for different clinical patterns, NC is the key feature of BA especially when associated with pale stool and dark urine in a healthy infant.

The biochemical features of the disease include direct hyperbilirubinaemia, raised liver transaminases, raised alkaline phosphatase and γ-glutamyl transpeptidase; however, these findings may overlap with many other causes of NC. Non-dilatation of biliary tract, absent or non-contractile gallbladder, positive triangular cord and sub-capsular hepatic flow, and right hepatic hypertrophy are the main findings by abdominal ultrasound that help in the diagnosis of BA [12]. The presence of bile duct proliferation, bile plug, a small cell infiltrate, and portal fibrosis and the absence of sinusoidal fibrosis and giant cells are the major histopathological findings in BA [13].

Duodenal aspiration and analysis for bile have been used for diagnosis of BA. Because of the poor differentiating rule of technetium-labelled iminodiacetic acid derivatives, this technique now is less commonly used. Endoscopic retrograde cholangiopancreatography is another recent tool for diagnosis of BA, but it highly invasive. On-table cholangiography remains the gold standard for diagnosis [14].

The usual management of BA is a surgical attempt to restore bile flow using the Kasai portoenterostomy (KPE) technique. The aim of KPE is to restore, albeit imperfectly, the residual intrahepatic biliary system with the gastrointestinal tract and delay the progress to liver fibrosis. In case of failure of KPE, LT should be considered [15].

Choledochal malformation (choledochal cyst [CC])

CC is a congenital dilation of the biliary tree not secondary to an obstruction. It is a benign condition but can be complicated by cholestasis, cholelithiasis, cholangitis, biliary cirrhosis, pancreatitis, and malignant transformation [16]. Females are four times as likely as males to experience CC [17]. The flux of pancreatic enzymes into the biliary tree is observed in one third to two thirds of patients due to anomalies in the pancreaticobiliary duct. Biliary epithelium exposure to these caustic enzymes may contribute to CC formation [18]. Abdominal pain, NC, and right upper quadrant mass are the classic presentation [19]. CC is classified as follows: type I, fusiform dilatations of the common bile duct (CBD); type II, true diverticula of the CBD; type III CC (choledochoceles), intraduodenal dilations of the common channel; type IVA CC, multiple IHBD/EHBD dilatations; type IVB CC, EHBD dilatation; and type V CC (Caroli's disease), cystic dilation of the IHBDs [20]. Abdominal ultrasound demonstrates abnormal dilatation of the CBD. Laboratory results reveal conjugated hyperbilirubinaemia, increased γ-glutamyl transpeptidase (GGT) level, and mild elevation of liver transaminase levels. Albumin and globulin levels are normal. It is essential to differentiate CC from cystic BA, and approximately one tenth of BA patients may have cystic components of EHBDs [21, 22]. Before

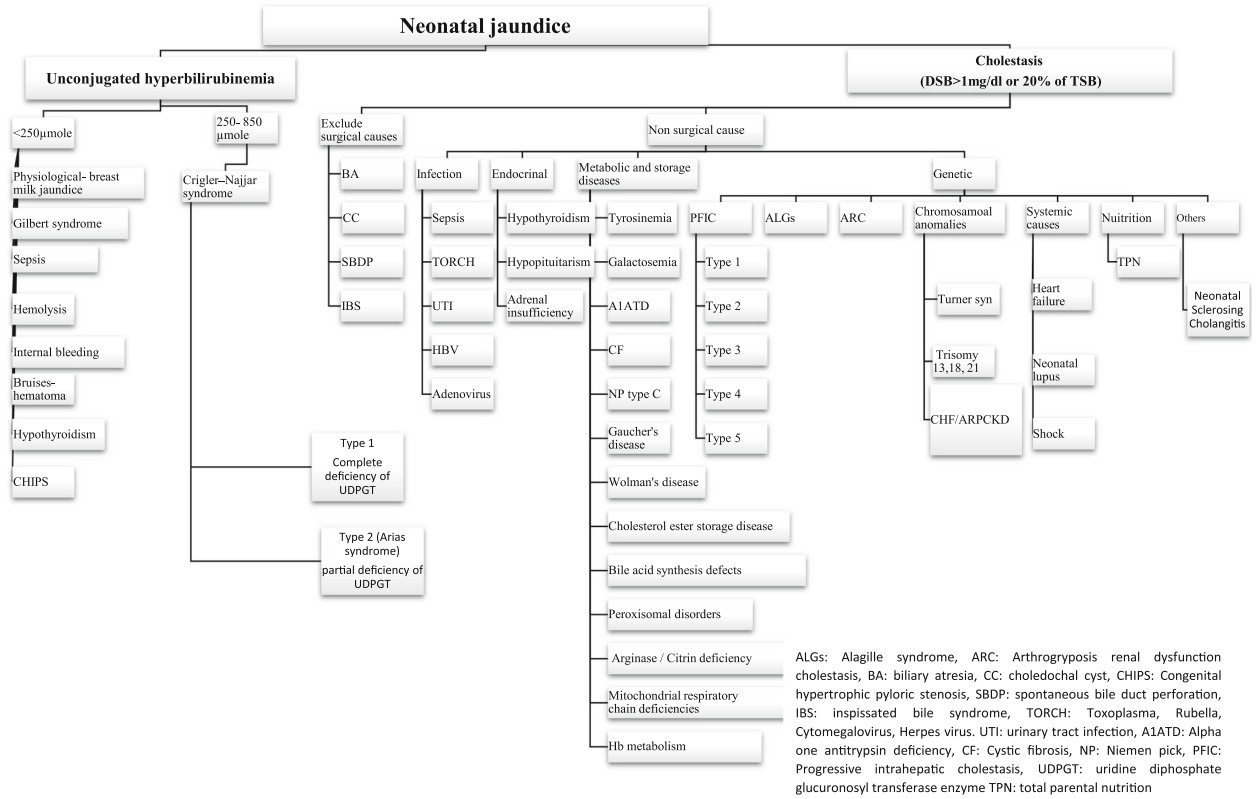

Fig. 1 Causes of neonatal jaundice

surgical intervention, the precise diagnosis should be reached, as this can affect the management strategy and prognosis [23]. Intraoperative cholangiogram and pathologic examination (absence of an epithelial lining and presence of a grossly visible inner cyst wall) can effectively differentiate between both entities [24, 25]. Surgical cyst excision is the treatment of choice [20]. Laparoscopic hepaticojejunostomy is a new feasible treatment option achieving a better outcome than traditional treatment modalities with fewer complications [26].

Inspissated bile syndrome (IBS)

IBS is a rare cause of NC resulting from the obstruction of the EHBDs by either bile plugs or sludge without chemical defects of the bile, anatomical abnormalities, or liver cell damage [27]. IBS accounts for 8% of the surgically treatable causes of NC, with an estimated incidence of 1/175,000 live births [28, 29]. Systemic infection, haemolysis, total parental nutrition (TPN), rapid weight loss, progressive familial intrahepatic cholestasis (PFIC), citrin deficiency, and drugs (ceftriaxone) can cause IBS [30]. IBS can resolve spontaneously with or without the administration of oral ursodeoxycholic acid (UDCA) (10–20 mg/kg). Failed medical management indicates the need for endoscopic retrograde cholangiopancreatography, percutaneous transhepatic cholangiography, or irrigation of the biliary tree with saline or a mucolytic agent through a cholecystostomy [30, 31]. Co-administration of N-acetylcysteine and glucagon can effectively treat IBS [32]. Omega-three polyunsaturated fatty acids (500 mg four times per day) can be used as an alternative to surgical intervention [27].

Spontaneous biliary duct perforation (SBDP)

SBDP is a rare disease involving the perforation of the bile ducts and gallbladder in the absence of CC, and it is commonly diagnosed in early infancy [33]. SBDP occurs at the confluence of the cystic and common hepatic ducts. The cause is mainly idiopathic, although some cases are associated with pancreaticobiliary malunion or distal CBD obstruction by either stones or atresia. Based on the site of perforation, most perforations are situated anteriorly (at the junction of the cystic duct and the CBD) and can be controlled by adjacent structures. If that control fails, bile leaks into the peritoneal cavity, resulting in bilious ascites [34, 35]. Clinically, patients complain of abdominal distension, vomiting, discoloration of hydroceles or hernia sacs, NC, and clay-coloured stool. Patients are usually healthy despite the presence of bilious ascites unless there is an associated infection. Persistent vomiting may be the only symptom

of posterior perforation. Less commonly, there is an acute deterioration associated with sudden abdominal pain, abdominal distension, fever, and vomiting [30].

SBDP can be treated conservatively with broad-spectrum antibiotics [36], endoscopic retrograde pancreatography [34], and percutaneous transhepatic cholangiography [37]. Failed conservative therapy indicates the need for surgical intervention (biliary intestinal reconstruction) [38]. Although SBDP has a good prognosis, it may be complicated by biliary fistulas or portal vein thrombosis [38, 39].

Non-surgical causes

Idiopathic neonatal hepatitis (INH)

INH is a term historically applied to infants presenting with idiopathic NC or neonatal hepatitis. There is an increasing number of identified aetiologies producing neonatal hepatitis or cholestasis including infectious and metabolic causes such as tyrosinemia, alpha-1 antitrypsin deficiency (A1ATD), and galactosemia [6]. INH represents 15% of the causes of NC, characterized histologically by the presence of giant cells and prolonged idiopathic intrahepatic cholestasis. Immature hepatocyte injury caused by infection, biliary obstruction, or metabolic disease results in multinucleated giant cell generation [40]. In addition to the elevated levels of GGT and alkaline phosphatase among BA patients, anti-smooth muscle antibodies are new biomarkers that are useful in differentiating between BA and INH. The antibody levels are significantly higher in patients with BA than in those with INH [41].

Infection

Sepsis Inflammatory mediators (i.e. bacterial endotoxin and lipopolysaccharides) cause NC by triggering the release of cytokines [42]. NC is considered to be a severe condition that may complicate neonatal septicaemia. Prolonged NC will aggravate liver dysfunction, leading to liver failure and the failure of other organs. Management of neonatal sepsis-associated NC at the early stage is mandatory to prevent its sequelae and maintain normal growth and development [43].

Infection Infection (toxoplasma, rubella, cytomegalovirus, and herpes simplex virus types 1 and 2) is an aetiological factor for NC, including BA [9, 44]. TORCH IgM antibodies were detected in 8.5% of patients with BA and in 23% of the non-BA group; cytomegalovirus is the most commonly diagnosed agent [45].

Metabolic disease

Alpha one antitrypsin deficiency (A1ATD) Alpha one antitrypsin (ATA) is a glycoprotein synthesized mainly by the liver. ATA is the main protease inhibitor (Pi) [46], protecting against lung damage by inhibiting the neutrophil elastase enzyme [47]. A1ATD is among the most common Mendelian hereditary liver disease in Caucasians, affecting 1/1800 live births [48]. Although A1ATD is a common disorder, it is underdiagnosed, especially in patients with liver disease [49].

In paediatric patients, BA is generally the most common indication for LT, and A1ATD is the most frequently identified genetic cause [47]. Among the known genetic variants (> 100), approximately 30 alleles have clinical implications [50]. The PiM gene is the normal gene; PiS and Piz are the most common deleterious genes [50, 51]. Abnormal proteins accumulate in hepatocytes, inducing hepatitis, hepatic fibrosis, and cirrhosis [52]. A1ATD should be considered when examining infants with NC. Genotyping is recommended irrespective of the serum A1AT concentration [53].

Galactosemia The process of galactose metabolism is illustrated in Fig. 2 [54]. Classic galactosemia is an autosomal recessive disorder [55] affecting 1/16,000–60,000 live births [56]. It presents during the neonatal period and is a potentially lethal disorder that can lead to chronically debilitating complications [57].

Clinically, patients are asymptomatic at birth; after a few days of galactose ingestion, they develop poor feeding, weight loss, vomiting, diarrhea, lethargy, malnutrition, failure to thrive (FTT) (the most common), and hypotonia. Untreated patients may develop hepatocellular damage, NC, severe hemolysis, and cataracts. Advanced cases develop life-threatening conditions, i.e. acute neonatal toxicity syndrome characterized by hypoglycemia, food intolerance, NC, hepatosplenomegaly, hepatocellular insufficiency, renal tubular dysfunction, hypotonia, and sepsis especially with gram-negative organism (E. coli is the commonest), pseudotumour cerebri with bulging fontanel, progressive liver disease, mental retardation, and ovarian failure [58, 59].

Reducing substances in urine that do not react with glucose oxidase as a method of newborn screening (NBS) can be an initial test; however, it is not totally valid [60]. High levels of red blood cell galactose 1 phosphate and/or galactitol (detected even after galactose restriction) in the blood and/or urine are more specific. Diagnosis should not be based mainly on elevated galactose 1 phosphate levels [> 10 mg/dl], as in benign variants, patients have a normal level [61]. The levels of galactose 1 phosphate should be measured 3 and 9 months after dietary restriction, and then yearly [62]. High urinary and serum galactitol levels are detected even after galactose restriction [63]. Low levels of red blood cell galactose-1-phosphate uridyltransferase (GALT) activity (≤ 10% of control activity) are diagnostic

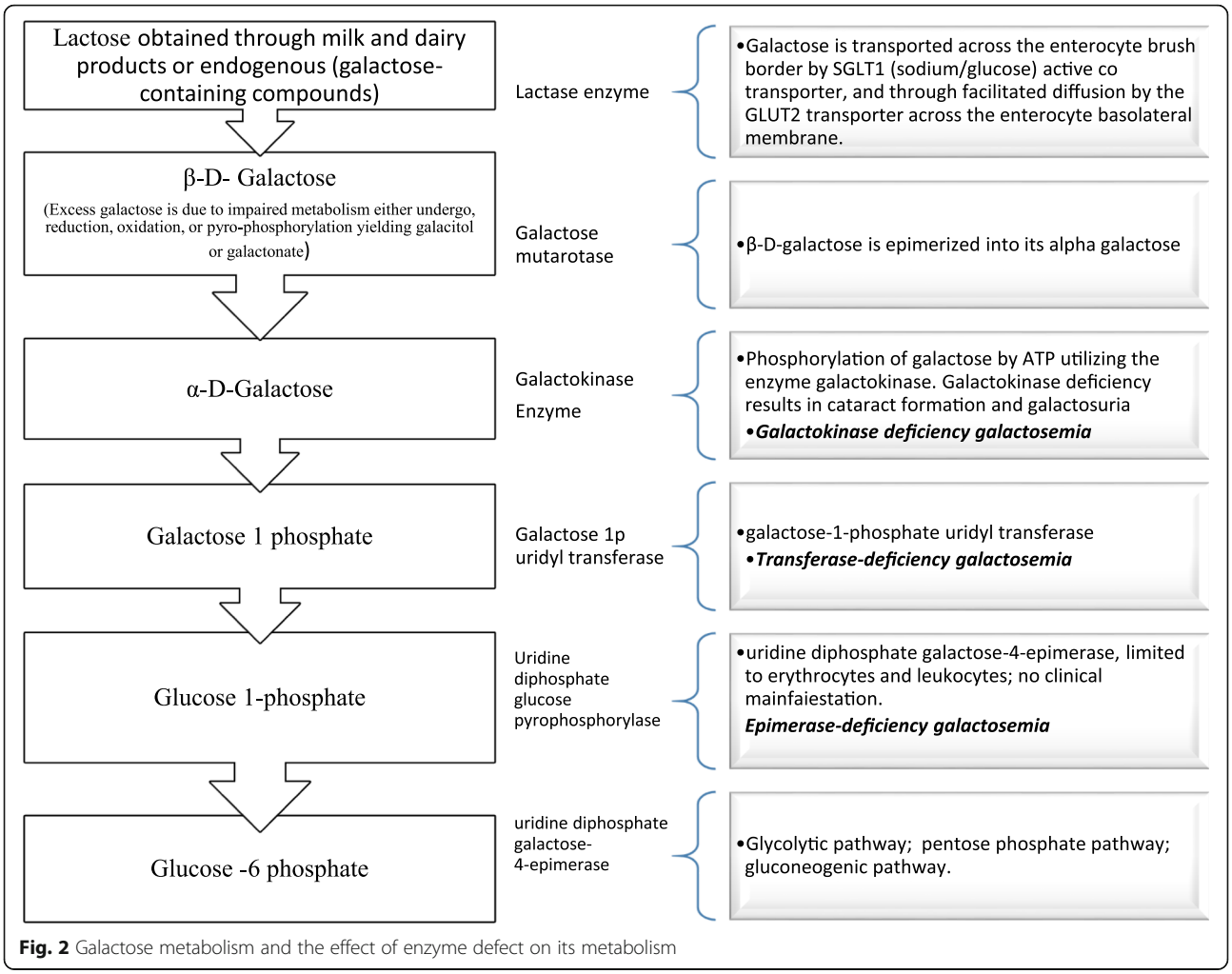

Fig. 2 Galactose metabolism and the effect of enzyme defect on its metabolism

for galactosemia. A negative result does not exclude the disease, and full gene sequencing may be required [64]. GALT mutational analysis has been used in some NBS programmes to improve screening outcome [65]. A life-long dietary lactose-free diet is the mainstay of treatment; however, this diet may be insufficient to prevent long-term sequelae [66]. Dietary restriction should be started even before confirming the diagnosis, and calcium and vitamin D should be supplemented. A galactose-free diet results in reversal of the acute symptoms and normal growth, with complete recovery of liver function. However, long-term sequelae such as speech impairments may persist into adulthood [62, 67]. The administration of an aldose reductase inhibitor is another treatment option because galactitol is an important pathogenic metabolite [68], but its role may be less efficient in galactokinase deficiency rather than in classical galactosemia [69].

Tyrosinemia I (TYR-1) (hepatorenal tyrosinemia) The process of phenylalanine metabolism is illustrated in Fig. 3 [70]. Tyrosinemia (type 1-III) is an autosomal recessive disease associated with a high level of blood tyrosine [71]. The three types of the disease differ genetically, enzymatically, and clinically, and TYR-1-associated liver dysfunction is a useful differentiating point [72]. TYR-1 results in symptoms before the second year of life; however, acute liver and renal dysfunction may manifest earlier [73]. Some patients present after their second birthday with isolated coagulopathy or other signs of liver dysfunction, renal tubular dysfunction, hypophosphatemic rickets, and FTT. Moreover, succinyl acetone inhibits aminolevulinate dehydratase, which causes bouts of abdominal pain, polyneuropathy, an increase in δ-aminolaevulinic acid in the urine, and other manifestations resembling acute intermittent porphyria [74]. Neurologic crises, manifesting as painful episodes affecting extremities and/or abdomen, accompanied by hypertension and hyponatremia, may present at any time and may result in respiratory failure and death [75]. Survivors may develop hepatomas that often transition to hepatocellular carcinoma (HCC), with a

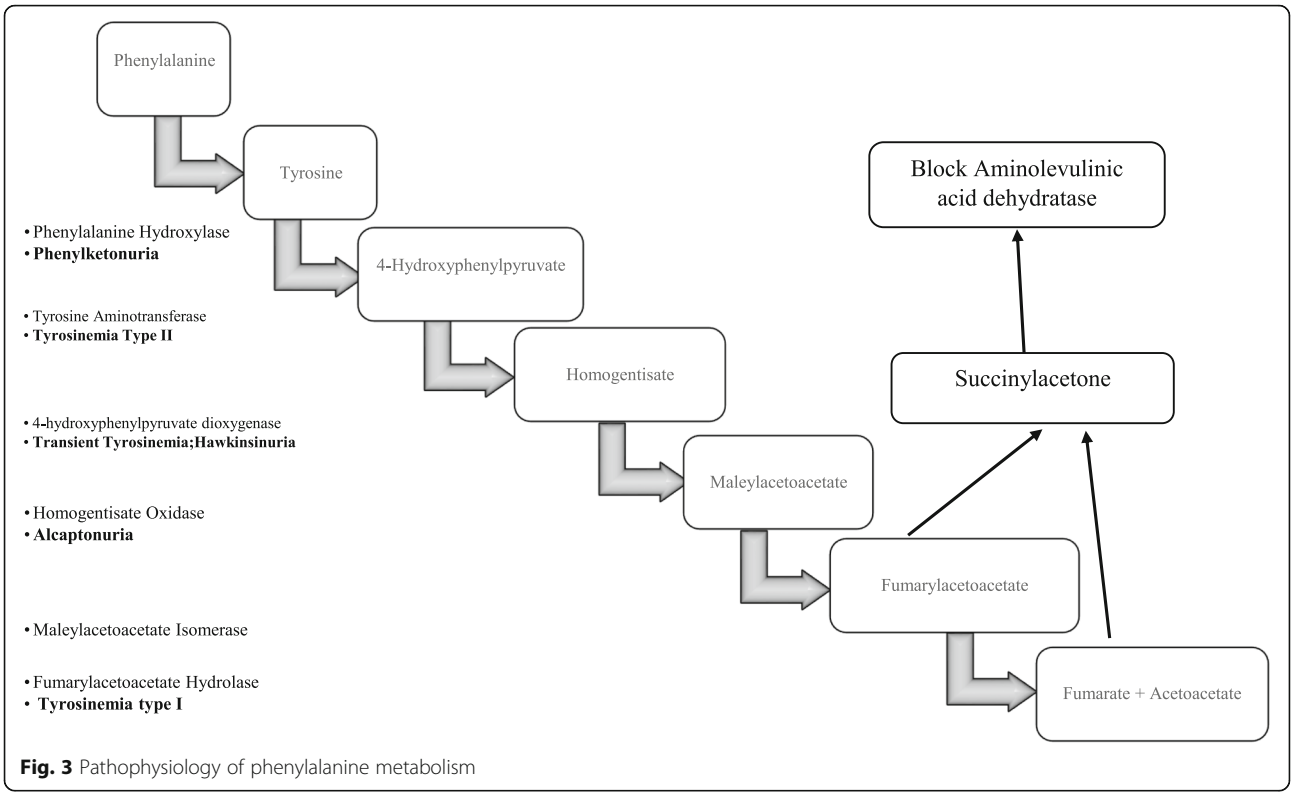

Fig. 3 Pathophysiology of phenylalanine metabolism

lifetime risk as high as 37% [76]. HCC may be the first recognized clinical event [77]. Newborns referred to metabolic centres for elevated tyrosine and/or succinyl acetone levels suspected of having TYR-1 should receive clinical and laboratory evaluations as soon as possible. NBS using blood/urinary succinyl acetone levels is predicted to identify all affected infants [78]. Plasma amino acids and liver function tests, including the prothrombin time, should be investigated. Patients should restrict their tyrosine and phenylalanine intake to maintain their plasma levels within the non-harmful range [73]. This prevents corneal tyrosine crystal formation. If the blood concentration of phenylalanine becomes too low (< 20 μmol/L), additional natural protein should be added to the diet [79]. Early treatment with nitisinone is associated with lower rates of LT, without any improvement in the neurological complications [80]. LT, as a treatment for TYR-1, is limited to patients who have developed malignancies or decompensated liver disease and in those who do not have access to or are refractory to nitisinone [81]. Successful LT is expected to restore liver function and reduce the risk of HCC [82].

Citrin deficiency Mutation of the human SLC25A13 gene encoding a mitochondrial aspartate/glutamate carrier isoform 2 can lead to its deficiency. The deficiency of this carrier results in neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD), FTT, dyslipidaemia (intermediate phenotype), and adult-onset fatal disease, namely, citrullinemia type II [83]. NICCD manifests early in infancy with NC, diffuse fatty liver, parenchymal cellular infiltration associated with hepatic fibrosis, hypoalbuminemia, coagulopathy, liver dysfunction with or without hypoglycaemia, and galactosemia. Citrulline levels are elevated in the early neonatal period, followed by increases in the levels of arginine, threonine, methionine, phenylalanine, tyrosine, and galactose [84–86]. The prevalence of NICCD is underestimated because of the majority of the affected infants die early or are misdiagnosed as having INH [85]. DNA analysis or Western blot analysis of defective proteins in lymphocytes are the most reliable diagnostic tools [87]. Dietary supplementation with a lactose-free formula, a medium- chain triglyceride-enriched formula, fat-soluble vitamins, UDCA, and phenobarbital is strongly recommended. LT is another treatment option in cases of medical treatment failure [84].

Cystic fibrosis (CF) CF is an autosomal recessive disease that results from a mutation in the CF transmembrane regulator (CFTR) [88]. Recently, a novel mutation of CF, c. 3871 G > T, was identified [89]. Classic CF manifests with pulmonary symptoms, meconium ileus, recurrent pancreatitis or pancreatic insufficiency, and focal biliary cirrhosis due to the obstruction of the IHBDs [90]. NC occurs more frequently in patients with

meconium ileus and TPN. The associated clay stool and conjugated hyperbilirubinaemia may result in a misdiagnosis of BA [91]. The abnormal expression of CFTR in the apical surface of the biliary epithelium affects bile fluidity and viscosity, resulting in abnormal bile accumulation [92, 93]. NC resolves, on average, by 9.2 months of age; if not, hepatobiliary complications will arise [94].

NBS can be accomplished by measuring the immunoreactive trypsinogen level in dried blood spot. If the result measured ≥ 62 ng/mL, testing for CFTR mutations through DNA sequencing is mandatory. Patients with ≥ 2 mutations are affected with the disease, and those with one mutation are diagnosed as carriers. This diagnostic approach had a sensitivity and positive predictive value of 92% and 34% respectively [90].

The mainstay of treatment is to delay the progression to cirrhosis and development of portal hypertension. Management of CF should include multi-speciality team, including pulmonologist, hepatologist, otolaryngology specialist, dietitian, radiologist, psychologist, and surgeon.

Poor nutritional intake is a common problem and caused by poor appetite, malabsorption, and increased caloric expenditure. If there is pancreatic insufficiency, evaluation of plasma levels of fat-soluble vitamins after the initiation of enzyme and vitamin supplementation 3–6 months after initiation or change in vitamin therapy and yearly subsequently should be done [95]. For more details on nutritional requirements for cholestatic patient please, read the article at https://www.sciencedirect.com/science/article/pii/S111066381730054X.

Reduction of hyperbilirubinaemia can be achieved either medically (UDCA 20–30 mg/kg body weight/day) or by cholangiogram. In addition to its immunoregulatory function, UDCA has a cytoprotective effect against toxic bile acids and it displaces them. Furthermore, UDCA stimulates calcium-activated chloride channels [96].

However, progression to stenosis and fibrosis of the hepatic ducts and CBD may occur, and surgical correction becomes necessary. LT is offered for patients with end-stage liver disease provided that there is any contraindication [93]. LT to treat CF-related liver disease accounted for 3.5% of all paediatric LTs over a 16-year period [94].

Bile acid synthesis disorders (BASDs) BASDs are disorders of primary bile acid (cholic and chenodeoxycholic acid) synthesis that result in liver injury due to the accumulated toxic intermediate metabolites. Abnormalities in bile excretion result in the retention of other toxic metabolites within the liver. BASDs should be included in the differential diagnosis of NC [97]. The effects of BASDs on the liver range from persistent cholestasis to acute hepatitis or liver failure. Clinically, patients present with NC, FTT, hepatosplenomegaly, rickets, evidence of fat malabsorption, and bleeding. Neurologic effects include seizures, developmental delay, deafness, blindness, and neuromuscular weakness [98]. UDCA disrupts serum bile acid levels, and liver transaminases are elevated with normal GGT. Urinary bile acids should be measured to identify the synthetic defect. Liver biopsy is not diagnostic [97]. Treatment with cholic acid, not ursodiol, suppresses the production of toxic metabolites and maintains normal growth and development [98].

Genetic causes

Alagille syndrome (ALGS) (arteriohepatic dysplasia, Alagille–Watson syndrome) is a multisystem autosomal dominant disorder. The majority of cases are caused by the JAG1 gene mutation [99]. NOTCH 1 mutations are diagnosed in < 1% of the cases, indicating a higher risk of renal disease [100]. ALGS affects the liver, heart, skeleton, eyes, kidneys, and central nervous system, and it leads to characteristic facial features [101]. ALGS is a rare disorder affecting 1/70,000 live births, based on the presence of neonatal liver disease; however, it is underestimated because that metric does not take into account the reduced penetrance of the condition [102]. In newborns, bile duct paucity may be present in conjunction with ductal proliferation, resulting in its misdiagnosis as BA [103]. However, before molecular genetic testing, variable expression can be determined through segregation analysis, and it has been suggested that the presence of only one feature is sufficient to make the diagnosis in extended family members [104] (Fig. 4). ALGS is now defined by both its genotype and its phenotype. Bile duct paucity is not a characteristic of ALGS, but it is present in trisomy 21, CF, congenital infections, A1ATD, and Zellweger and Ivemark syndromes [101]. All patients should undergo liver and renal function tests, lipid profiling, serum bile acids tests, and clotting studies. Ophthalmic examinations, spinal X-rays, abdominal ultrasounds, echocardiographs, scintiscans, and liver biopsies may be needed in ALGS patients to diagnose systemic complications. All patients should undergo regular growth monitoring, receive nutritional support, and have meticulous renal and pancreatic function follow-up [101]. Fortunately, intense pruritus due to associated liver disease can be treated with choleretic agents such as UDCA, cholestyramine, rifampicin, or naltrexone. Biliary diversion is a helpful procedure and can be beneficial before LT. In certain cases, partial external biliary diversion has also been demonstrated to be successful [105]. The success of the LT is affected by the associated comorbidities [106].

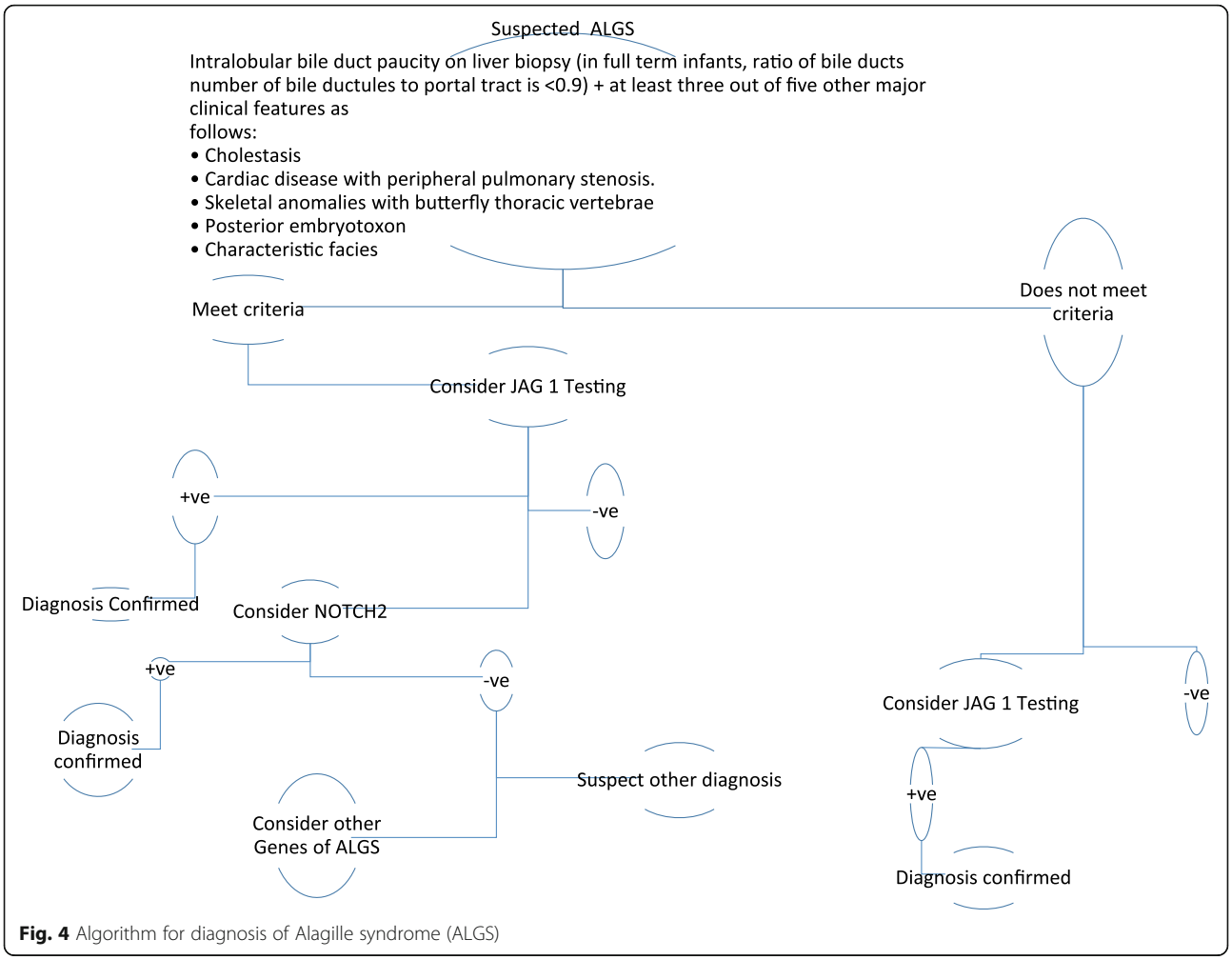

Fig. 4 Algorithm for diagnosis of Alagille syndrome (ALGS)

Progressive familial intrahepatic cholestasis (PFIC) PFIC is a heterogeneous group of rare, autosomal recessive disorders resulting from defects in the mechanisms involved in bile formation with typical clinical, biochemical, and histological features. PFIC presents with intrahepatic cholestasis in infancy or childhood [107]. The worldwide incidence is 1/50,000 to 1/100,000, with equal distribution between the sexes [108]. The course of the disease involves portal hypertension, liver failure, cirrhosis, and HCC along with several extra-hepatic manifestations. The five types of PFIC are identified in Table 1 [109, 110].

Arthrogryposis renal dysfunction cholestasis (ARC) syndrome ARC syndrome is a rare fatal autosomal recessive multisystem disorder involving the liver, kidney, skin, central nervous system, and musculoskeletal system; it is caused by mutations in the VPS33B or VIPAR gene [111]. ARC syndrome includes arthrogryposis (muscle atrophy, radial deviation of the wrist, dislocation of both hip joints, flexion contracture of the knee joints, and calcaneo-valgus), renal tubular acidosis, and NC [112]. Half of the cases have ichthyosis, and one fourth of those with ARC syndrome may have platelet anomalies. Agenesis of the corpus callosum is reported in more than one fifth of cases. One tenth of patients with ARC syndrome have congenital cardiovascular anomalies, deafness, recurrent infections, and internal bleeding due to coagulation dysfunctions. Mild or atypical symptoms may delay diagnosis. The prognosis of ARC syndrome is poor, and the majority of patients die during infancy [113]. The pathogenesis characteristic of ARC syndrome primarily involved degeneration of the anterior motor neurons, whereas the severity of arthrogryposis may be traced to placental insufficiency during pregnancy, with oligohydramnios in the mother and foetal growth restriction. Osteopenia and pathological fractures are attributable to impaired renal tubular reabsorption and secondary hyperparathyroidism [114]. Renal tubular dysfunction manifests in the form of Fanconi syndrome, renal tubular acidosis, nephrogenic diabetes insipidus, glucosuria, aminoaciduria, and phosphaturia [114]. In

Table 1 Characteristic features of the different types of progressive familial intrahepatic cholestasis [102–104]

Item	PFIC 1 Byler disease	PFIC 2	PFIC 3	PFIC 4	PFIC5
Both genders are equally affected, incidence 1/50000–100,000					
Genetics					
Inheritance	AR	AR	AR	AR	AR
Gene	ATP8B1/F1C1	ABCB11/BSEP	ABCB4/MDR3	TJP2	NR1H4
Protein	Familial intrahepatic cholestasis 1 (FICl)	Bile salt export protein (BSEP)	Multidrug resistance protein 3 (MDR3)	TJP2 protein	FXR, the key regulator of BS metabolism
Chromosome	18q21-q22	2q24	7q21	9q12	12q23.1
Location	Wide tissue distribution including almost all epithelial cells; on apical membranes	Hepatocyte canalicular membrane	Hepatocyte canalicular membrane	Tight junctions	Bile canaliculi, FXR is highly expressed in liver and pancreatic β cells
Pathophysiology					
Function of hereditary defect	Aminophospholipid flippase	Bile acid secretion	Phosphatidylcholine secretion	Integral tight junction protein (claudin-1)	Farnesoid X receptor loss
Clinical findings					
Age of onset	Neonates	Neonates	1 month–20 years	Infancy, childhood	Neonate
Course	Progressive	Progressive	Progressive	Progressive	Rapidly progressive
Cholestasis	Chronic	Chronic	Chronic	Chronic	Chronic
Pruritus	Severe	Severe	Moderate	Severe	Severe
Others	Other features include short stature, diarrhoea, hepatosplenomegaly, malabsorption, pancreatitis, respiratory disease, and occasionally sensorineural hearing loss	Growth failure gallbladder stones	Later onset cholestasis, portal hypertension, minimal pruritus, gall bladder stone, cupper accumulation in liver tissue, and increase in urinary cupper.	Intrahepatic cholestasis, early childhood liver failure, portal hypertension, neurological and respiratory symptoms	Coagulopathy a direct consequence of the loss of FXR function. Failure to thrive and ascites, gallstones pleural effusions, and intraventricular haemorrhage at birth
Risk of malignancy	–	+ HCC/ cholangiocarcinoma (in 30% of patients)	+	+ HCC	
Laboratory findings					
Serum GGT	Normal/low	Normal/low	High	Normal or mildly increased	Low to normal
Serum ALT	Mildly elevated	> 5 × normal	> 5 × normal	Elevated	Elevated
Serum AFP	Normal	Elevated	Normal	Elevated	Elevated
Serum primary bile acid concentration	Very high + normal cholesterol	Very high	High		
Biliary bile acid secretion	Low	Low	Low		
Liver biopsy					
Histology	Minimal giant cell transformation, intracanalicular cholestasis, no ductal proliferation, minimal inflammation. Late fibrosis	Giant cell transformation, intracanalicular cholestasis, no ductular proliferation, moderate inflammation, fibrosis, extramedullary hemopoiesis	Giant cell transformation, intracanalicular cholestasis, ductular proliferation, moderate inflammation, marked fibrosis, lipid crystals within bile ducts, and fibroobliterative bile duct lesions	Ductular reaction, diffuse giant cell transformation, and ballooning of hepatocytes and intralobular cholestasis	Intralobular cholestasis, diffuse giant cell transformation, ballooning hepatocytes, and ductular reaction. Micronodular cirrhosis and fibrosis were evident at

Table 1 Characteristic features of the different types of progressive familial intrahepatic cholestasis [102–104] *(Continued)*

Item	PFIC 1 Byler disease	PFIC 2	PFIC 3	PFIC 4	PFIC5
					later stages
Electron microscopy	Byler type coarsely granular bile; loss of microvilli, swollen microvilli	Amorphous filamentous bile; loss of microvilli	Presence of cholesterol crystals; loss of microvilli, bile is dense and amorphous.	Elongated tight junctions between adjacent hepatocytes and biliary canaliculi seen on biopsy	
Immunohistochemistry	BSEP positive	BSEP negative	BSEP positive		BSEP negative
	MDR3 positive	MDR3 positive	MDR3 negative		MDR3 positive
	GGT negative	GGT negative to weakly positive	GGT positive		GGT positive
Treatment					
	UDCA, rifampin fat-soluble vitamins + biliary diversion, ileal exclusion, liver transplantation; post-orthotropic liver transplantation diarrhoea, pancreatitis, steatorrhea, fatty liver with possible progression to cirrhosis	Biliary diversion, liver transplantation (possible recurrent disease after transplantation)	UDCA if residual PC secretion; liver transplantation	Liver transplantation	Liver transplantation

AR autosomal recessive, *GGT* gamma-glutamyl transferase, *AFP* alpha fetoprotein, *ALT* alanine aminotransferase, *BSEP* bile salt export pump, *UDCA* ursodeoxycholic acid, *HCC* hepatocellular carcinoma

the absence of biliary obstruction, patients with hepatomegaly and NC with low GGT levels and normal or slightly elevated liver enzymes are characteristic of ARC. It is recommended that patients with low GGT levels and conjugated hyperbilirubinaemia associated with ichthyosis, deafness, platelet dysfunction, and central nervous system malformations should be tested for VPS33B mutations [115]. A paucity of bile ducts, giant cell transformation, bile plugs or lipofuscin deposition, and portal fibrosis differentiate ARC from BA [116]. At present, there is no specific treatment for ARC syndrome; supportive care includes intravenous fluids, anti-infection measures, and supplementation with UDCA, fat-soluble vitamins, calcium glubionate, L-thyroxine, and phosphate. Nevertheless, immediate orthopaedic intervention for patients with joint contractures, congenital hip dislocations, and a vertical talus may be required. Aggressive orthopaedic management is not recommended because the patient's poor overall status and the low survival rate may affect the outcome of the surgery [117]. In cases of the failure of medical therapy, it is advisable to consider LT to improve severe cholestasis and intractable pruritus [111].

Nutrition: total parenteral nutrition-associated cholestasis (TPN-AC) NC is a frequently reported complication of TPN [6]. TPN-AC is diagnosed if there is persistent conjugated hyperbilirubinaemia greater than 2.0 mg/dL for at least two consecutive tests during TPN, with the absence of any other causes of NC [118]. The exact aetiology is not known; risk factors associated with TPN-related cholestasis are very low birth weight, prematurity, the duration of TPN, sepsis, the absence of enteral feeding, the quality or quantity of amino acid intake, male sex, trace mineral or phytosterol toxicity, and perinatal depression or shock [119–121]. Intestinal resection and its complications have also been associated with the occurrence of TPN-AC [122]. The severity of the disease varies from mild to severe, and it can lead to significant hepatic injury and end-stage liver disease. The histopathological changes are correlated with the duration of TPN [123, 124]. A shortened TPN course and early initiation of enteral feeding can effectively decrease the frequency of NC. UDCA (10–30 mg/kg/day) is the most widely used drug in the treatment of TPN-AC [125].

Wolman's disease Wolman's disease is a fatal autosomal recessive disorder representing the infantile form of lysosomal acid lipase deficiency. Patients usually do not survive beyond infancy. There are two different phenotypes that lie on a clinical continuum, depending on the amount of functional enzyme that is produced in vivo [126]. Clinically, Wolman's disease presents with hepatomegaly, FTT, diarrhoea, vomiting, malabsorption haemophagocytic lymphohistiocytosis, and liver failure

[127]. The exact disease incidence is unknown but is estimated to be approximately 1/500,000 live births [128]. There is no or very minimal lysosomal acid lipase activity (< 1% of normal), resulting in heavy accumulation of cholesteryl esters and triglycerides in visceral organs, i.e. liver and bone marrow, which means that patients usually present within the first 2–4 months of life [128, 129]. Adrenal infiltration is leading to necrosis and calcification of the adrenal glands in approximately 50% of patients. Intestinal involvement results in chronic diarrhoea or steatorrhea secondary to the disease process itself and the resultant severe malabsorption [129]. Oxysterol levels are a new biomarker for the diagnosis of Wolman's disease and are correlated with the clinical management of the disease [130]. Intestinal malabsorption, hepatic impairment, and adrenal insufficiency explain the very poor prognosis of these young patients [131].

Management

General medical management

Most children having NC are malnourished and require an adequate provision of caloric requirements to prevent and treat malnutrition associated with steatorrhea and malabsorption. Affected patients should receive 125% of the recommended dietary allowance based on ideal body weight [132]. Medium-chain triglyceride oil should be administered in a dose of 1–2 mL/kg/d in 2–4 divided doses in expressed breast milk. In non-breast feed, a mixture of puffed rice powder and MCT to milk can make feeds energy -dense. Essential fatty acids should constitute 2–3% of the energy provided. Vegetable protein at 2–3 g/kg/d is recommended. 1,25-Dihydroxyvitamin D_3 (0.05–0.2 μg/kg/d) is recommended in the presence of significant bone changes or patients having severe cholestasis. Vitamin K is administered at a dose of 5 mg intramuscular, subcutaneously or intravenously, at diagnosis to correct the coagulopathy. Water soluble vitamins are given orally 1–2 times the recommended daily allowance. Vitamin supplementation should be continued till 3 months after resolution of jaundice [133].

Specific treatment

Special infant formula and diets are recommended for children with specific diagnosis (galactosemia, fructosemia, and tyrosinemia). Treatment with nitisinone (1 mg/kg/d) in addition to dietary restriction leads to rapid reduction of toxic metabolites in tyrosinemia. Specific therapy is recommended for patients with CMV, herpes, and toxoplasmosis-related NC. Antibiotics need to be administered in patients with bacterial sepsis based on the site of infection and the performed culture. There is no role for steroids in INH.

In infants with pruritus due to severe cholestasis, UDCA (20 mg/kg/d), rifampicin (5–10 mg/kg/d), and phenobarbitone (5–10 mg/kg/d) are drugs of choice. Kasai's operation entails removal of the atretic extrahepatic tissue and a Roux-en-Y jejunal loop anastomosis to the hepatic hilum. Patients' bilirubin normalizes after KPE if it was performed before the end of the third month [134]. About 20% of all patients undergoing KPE during infancy survive into adulthood with their native liver [135]. In children with PFIC without decompensated cirrhosis, external and internal biliary diversion has been shown to be of benefit [136].

Liver transplantation

Liver transplantation is the standard therapy for decompensated cirrhosis due to any cause, and it is now well established. Any baby who has had failed KPE (bilirubin remains > 2 mg/dL, 6 months after surgery) should be referred to a transplant centre.

Conclusion

NC may be misdiagnosed as physiological jaundice; this may delay the proper management of the underlying disease and aggravates its complications. General practitioner and health care workers should be able to differentiate between physiological jaundice and NC especially BA; consequently, they would refer the affected patients to pediatric hepatologist as early as possible. In addition, parents must know when they should seek medical advice and when to suspect NC.

Abbreviations

A1ATD: Alpha-1 antitrypsin deficiency; ALGs: Alagille syndrome; ARC: Arthrogryposis renal dysfunction cholestasis; BA: Biliary atresia; BASDs: Bile acid synthesis disorders; CBD: Common bile duct; CC: Choledochal cyst; CF: Cystic fibrosis; CFTR: Cystic fibrosis transmembrane regulator; EHBDs: Extra-hepatic bile ducts; FFT: Failure to thrive; GALT: Galactose-1-phosphate uridyltransferase; GGT: Gamma-glutamyl transpeptidase; HCC: Hepatocellular carcinoma; IHBDs: Intrahepatic bile ducts; INH: Idiopathic neonatal hepatitis; KPE: Kasai portoenterostomy; LT: Liver transplantation; NBS: Newborn screening; NC: Neonatal cholestasis; NICCD: Neonatal intrahepatic cholestasis caused by citrin deficiency; PFIC: Progressive familial intrahepatic cholestasis; TPN: Total parental nutrition; TPN-AC: Total parenteral nutrition-associated cholestasis; UDCA: Ursodeoxycholic acid

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