Drug-Induced Liver Injury in Paediatrics: A Short Review

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Abstract: Drug-induced liver injury (DILI) is an under-recognized cause of paediatric liver disease. Although DILI in children accounts for about 1% of all reported adverse drug reactions throughout all age groups and less than 10% of all clinical DILI cases, it is responsible for about 20% of acute liver failure (ALF) cases. A wide range of drugs, herbal products and nutritional supplements have been associated with the development of DILI through dose-dependent, idiosyncratic or indirect mechanism. Limited literature is available in pediatric population, making DILI a still challenging diagnosis. An accurate medical history is of pivotal importance and should investigate about drug consumption, clinical and laboratory findings, individual and family risk factors for drug-related side effects or comorbidities, the timing of the injury onset after the implicated agent has been started (latency). Clinical presentation of DILI varies from asymptomatic or very mild to serious and sometimes fatal conditions; laboratory tests may be helpful in ruling out other causes of liver injury but, with few exceptions, they are aspecific. Early suspicion and prompt withdrawal of the offending drug play a key role for a successful management of most cases.

Rarely a specific therapy is available, as for acetaminophen toxicity, treated with N-acetylcysteine, and sodium valproate toxicity, where carnitine may be beneficial. Although controlled trials are not available yet, corticosteroids and ursodeoxycholic acid can be considered if no improvement is proven after discontinuation of drug.

The present short review is not intended to deal with all aspects concerning DILI but to focus on epidemiology, pathogenesis, clinical features, practical management and current challenges in paediatric age.

Keywords: Acetaminophen, Acute liver failure, Children, Drug-induced liver damage, Hepatotoxicity, Valproate.

INTRODUCTION

Drug Induced Liver Injury (DILI) accounts for approximately 10% of all adverse drug reactions (ADR) and it is the most common cause of acute liver failure (ALF) in Western Countries [1-2]. DILI in children accounts for about 1% of all reported ADR throughout all age groups and less than 10% of all clinical DILI cases but it is responsible for about 20% of ALF paediatric cases, mainly due to acetaminophen, antiepileptic drugs and antibiotics [3]. Although the incidence of DILI in the paediatric population is still not well defined, as many cases are not recognized or have a subclinical course, there has been an increasing concern in recent years [4]. In adults, for whom more systematic data are available, DILI occurs in 14 to 19 cases per 100,000 persons every year [5-6]. In children, a lower incidence is expected because of low occurrence of leading causes of hepatotoxic damage, such as drug consumption, alcohol abuse or exposure to cigarette smoke.

PATHOGENESIS

Three distinct phases of drug metabolization and excretion in the liver can be described [7]:

• Phase 1 (Activation): Cytochrome P450 (CYP450) enzymes own the ability to insert one atom from molecular oxygen into the medication molecule, producing a more soluble in water but also toxic compound.

• Phase 2 (Detoxification): Conjugating enzymes further increase solubility in water and neutralize toxicity of the Phase 1 metabolites.

• Phase 3 (Excretion): Finally the hydrophilic compounds are transported into the canalicular spaces for secretion with the bile.

In most cases DILI is caused by the accumulation of Phase 1 metabolites, following two different pathogenic mechanisms: intrinsic hepatotoxicity or idiosyncratic hepatotoxicity [8].

The first mechanism, so-called dose dependent, is caused by drugs or substances intrinsically toxic to the liver, with constantly reproducible and predictable effects related to the amount of drug exposure. Acetaminophen, which is widely used in paediatrics, acts with a dose dependent mechanism. Although its use at therapeutic doses is safe, an overdose still represents one of the main causes of ALF [9]. At therapeutic doses, paracetamol is metabolized via phase 2 metabolic reactions of sulfation and glucuronidation. At higher doses, phase 2 cofactors are depleted and a larger portion of acetaminophen is

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E-ISSN: 2311-8687/22

metabolized by CYP450 enzymes, producing the toxic metabolite N-acetyl-iminoquinone (NAPQI). NAPQI is initially detoxified by glutathione; however, once glutathione stocks are depleted, NAPQI binds to cellular protein macromolecules causing cell damage and necrosis [9]. A single dose of 150 mg/kg is capable of determining acute toxicity. Literature also reports cases of subacute acetaminophen hepatotoxicity related to accumulation of repeated doses over 24 hours [10].

The second pathogenetic mechanism, as well as the most frequent, is the idiosyncratic damage, unpredictable and not easily reproducible in animal models. Idiosyncratic DILI may occur after increasing the dosage of the drug, suggesting the existence of a threshold dose for each patient susceptible to damage [11]. The idiosyncratic patterns of DILI underlie a multifactorial pathogenesis: factors related to the drug (chemical structure, molecular weight, bioavailability), individual factors (age, sex, polymorphisms of HLA and non-HLA genes) and environmental factors (obesity, multiple drug therapy), leading to biochemical pathways blocking, altered canalicular transport of bile, or formation of immunogenic complexes [12].

A third mechanism, called indirect, has emerged, involving immune mediated injury to hepatocytes through the activation of T-cell response [13].

ASSOCIATED DRUGS

Several drugs, herbal products and nutritional supplements have been associated with the development of DILI. In literature, few case reports or case series of DILI are described in childhood, mostly associated with antipyretics, anti-inflammatories and antibiotics but also antiepileptics, antituberculosis, antineoplastics and unconventional drugs [14]. According to adult studies, DILI is often due to a combination of drugs in children and antibiotics are the most commonly implicated drug class [15]. Moreover, the class of the offending drug is largely dependent upon regional distribution. In the prospective multicenter Drug-Induced Liver Injury Network (DILIN) Study from the United States (US), antimicrobial agents and central nervous system (CNS) drugs have been found to be responsible for 50% and 40% of DILI, respectively [16]. Among the antimicrobials, minocycline caused the majority of DILI, being implicated in 13% of the episodes. In CNS group, antiepileptics (lamotrigine, valproate and phenobarbital) have been involved in 20% of DILI cases, drugs for attention deficit hyperactivity disorder (atomoxetine, methylphenidate) in 13% and antidepressants (fluoxetine, amitriptyline and perphenazine) in 7%. Only one DILI case have been triggered with herbal and dietary supplements.

Conversely, complementary/alternative drugs and anti-tubercular agents have been reported as prevalent groups of drug implicated in DILI in India (39% and 33%, respectively) [17]. Furthermore, chinese herbal medicine represents the main etiological agent of pediatric DILI in China [15].

Figure **1** shows a non-exhaustive list of drugs and their pathogenetic mechanism of damage.

CLINICAL PRESENTATION

Clinical features of DILI encount an extremely broad spectrum, being able to run subclinically, causing a slight increase in liver enzymes or acute and chronic liver disease which may vary from mild to severe damage, up to liver failure. DILI should always be considered in differential diagnoses, especially when facing severe elevations in aminotransferases and cholestatic liver damage in patients with normal hepatobiliary imaging.

Dose dependent	Idiosyncratic
Acetaminophen	Phenytoin
Ureidopenicilline (piperacilline)	Valproic acid
Aspirin	Amoxicillin-clavulanic acid
Amiodarone	Minocycline
Metotrexate	
Ciclophosphamide	

Figure 1: Main drugs involved in reports of hepatotoxicity in pediatric age and their mechanism of action.

The symptoms and signs of DILI reflect the different types of hepatic cells affected by the damage. In case of hepatocellular injury, children often show malaise, nausea, vomiting, anorexia, abdominal pain, mainly in the right hypochondrium, and elevated transaminases.

On the other hand, if cholangiocytes are damaged, the clinical presentation is characterized by itching and jaundice. Endothelial cells can also be affected causing ascites, hepatomegaly and increased bilirubin values [18]. Furthermore, when drug metabolites trigger an immune-allergic response, fever, rash, arthralgia, and facial edema can occur. More often, DILI affects several cell types within the liver, resulting in a mixed hepatic-cholestatic clinical picture. If untreated, DILI may lead to liver fibrosis, cirrhosis, liver failure and death [19].

DIAGNOSIS

DILI is primarily a clinical diagnosis but also a diagnosis of exclusion. If DILI is suspected, other possible causes of liver disease, such as infection by hepatotropic viruses (Hepatitis A, B, C and E, Cytomegalovirus, Epstein Barr virus), autoimmune hepatitis and intra or extrahepatic biliary diseases should be excluded. Subsequently, the patient or parent/caregiver should be asked for the following questions in order to detect an accurate medical history: drugs or other products consumption in the 6-8 weeks prior to the onset of clinical symptoms or laboratory alterations; total dosage of drug consumed and method of administration; description of the symptoms presented; any individual risk factors, such as previous drug reactions, family history of drug-related side effects, multiple drug therapy and any comorbidities; temporal relationship between the onset of symptoms and drug intake, emphasizing that a latency period may vary from days to months or years. Nevertheless, most of the DILI cases occur in the first 6 months after a drug consumption. Clinical signs of DILI may present even after discontinuation of the drug, as in case of amoxicillin-clavulanic acid which can trigger liver damage 1-6 weeks after the last dose [20].

A further diagnostic confirmation is given by regression of symptoms after the withdrawal of the drug; the recurrence of symptoms after reintroduction of the drug, the so called *rechallenge*, would confirm the diagnosis but it is not recommended because of an increased risk of developing severe liver disease [21].

Regarding DILI diagnosis, several semi-quantitative scales have been proposed, among which the Roussel Uclaf Causality Assessment Method of the Council of International Organization of MedicalSciences (RUCAM/CIOMS) is the most used. These scales, despite their relative simplicity, are not commonly used in pediatrics since their items are not specific for children: age, laboratory parameters which are variable in the growth period (such as alkaline phosphatase) and patient characteristics poorly suitable for pediatric age (alcohol abuse, pregnancy, cardiovascular disease) [22].

Laboratory tests are useful for diagnosis and follow up of liver damage [23]. Serum transaminases increase in hepatocellular injury, while alkaline phosphatase, conjugated bilirubin and/or gamma-glutamyl transpeptidase raise in cholestatic damage. Peripheral eosinophilia may also be present.

Drug-specific plasma concentrations can be detected for certain medication, as for acetaminophen: the Nomogram of Rumack and Matthew calculates the probability of liver damage based on the levels of paracetamolemia and the time passed since ingestion [24]. In other cases, autoantibodies can be relieved as in DILI after halothane administration [25].

Hepatic histology is the gold standard for determining the hepatocellular or cholestatic nature of the lesions and the severity of the damage, allowing the exclusion of some differential diagnoses (*e.g*. autoimmune hepatitis) [26].

The diagnosis of DILI must be questioned in the event of lack of clinical and laboratory improvement after discontinuation of the drug.

TREATMENT AND PROGNOSIS

Once the diagnostic suspicion of DILI is confirmed, discontinuation of the drug is usually recommended. In addition to supportive therapy, indicated in any case of hepatic insufficiency, N-Acetylcysteine (NAC) for acetaminophen and L-carnitine for valproate can be used as an antidote. Regarding NAC therapy, different treatment protocols have been proposed over the last decades; the most used scheme provides the administration of NAC 150 mg/kg in continuous infusion in the first 15-60 minutes, 50 mg/kg in the following 4 hours and 100 mg/kg in the following 16 hours [27]. The recently updated Australian and New Zealand guidelines propose treatment in two successive infusions (200 mg/kg in 4 hours, then 100 mg/kg in 16 hours) [28]. The US protocols recommend the administration of repeated oral doses for 72 hours,

while the European ones suggest the intravenous administration of NAC for a minimum duration of 20 hours [29]. The duration of the treatment is also controversial: for some authors NAC has to be practiced only in the first 24 hours of hospitalization while others suggest to prolong therapy up to 72 hours or to normalization of hepatic cytolysis indices. The effectiveness of NAC therapy depends on the early treatment, which prevents the accumulation of the toxic metabolite; the maximum benefit is obtained if administered within 8 hours, while it is reduced if therapy is started after 10-16 hours. However, the administration of NAC should never be omitted, even after an interval of 24 hours or more.

In case of acute toxicity after valproate ingestion, carnitine at a dose of 100 mg/kg intravenously over 30 minutes (maximum dose 6 grams) is recommended, followed by 15 mg/kg every 4 hours until clinical improvement. Other promising therapeutic strategies in valproate hepatic injury, include the administration of exogenous coenzyme A, NAC, vitamin U, zinc and selenium, in order to limit the damage from oxidative stress [30].

Scarce evidence is available about the efficacy of ursodeoxycholic acid in drug-induced liver damage, even if some case reports point out encouraging data. The use of steroids should be reserved for suspected immune-mediated DILI [31]. However, further studies are needed to test the efficacy and safety of ursodeoxycholic acid and steroids in drug-induced hepatotoxic damage.

The prognosis is highly variable and partly dependent on the drug involved and host factors. It has been shown that the best prognosis is associated with acetaminophen toxicity, with complete recovery in 90-94% of cases cured, while 6% of patients need for hepatotransplantation or dye [32-33]. A worse prognosis may occur in case of comorbidities or specific genetic profile, such as in valproate toxicity which can be severe for subjects less than two years old, on antiepileptic multiple therapy or suffering from mitochondrial diseases, homozygous POLG mutations or Alpers syndrome [30].

In most cases, a complete recovery of DILI is achieved after the discontinuation of the medication over a period ranging from days to months. A progression towards chronic DILI may reach 20% of cases [15]. Since ALF accounts about 20% of DILI complications in paediatrics, any children with suspected drug-induced liver damage presenting coagulopathy, encephalopathy and/or hypoglycemia should be immediately referred to a pediatric liver transplant center.

As signs of liver damage may persist over a long time, all patients diagnosed with DILI should be followed up until the normalization of laboratory values and complete recovery of clinical symptoms.

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Received on 31-12-2021 Accepted on 20-01-2022 Published on 01-02-2022

DOI: https://doi.org/10.12974/2311-8687.2022.10.1