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Cefuroxime-Induced Hepatocellular-Cholestatic Hepatitis with Pancytopenia

Wolfgang Kunze[1], Jan-Peter Streidl[1*], Thorsten Klemm[2], Juliane Lutze[1]

[1] Department of Children and Adolescent Medicine, Community Hospital Wurzen, Wurzen, Germany
[2]MVZ Laboratory Dr. Reising-Ackermann and Colleagues, Leipzig, Germany
Email: kunze@krankenhaus-muldental.de, *jan-peter.streidl@krankenhaus-muldental.de, t.klemm@labor-leipzig.de, juliane.lutze@gmail.com

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Abstract

Drug-induced liver injury is a rare event. We report on a 15-year old girl developing jaundice and a maculopapular rash with pruritus after oral cefuroxime therapy. Liver enzymes as well as total bilirubin and direct bilirubin were elevated. After eliminating other causes of hepatitis, cefuroxime-induced hepatocellular-cholestatic hepatitis with pancytopenia was diagnosed and cefuroxime therapy was stopped. The patient recovered quickly and was discharged without complications. The prognosis of this side-effect of cefuroxime is generally favourable; lethal courses are rare.

Subject Areas

Microbiology

Keywords

Cefuroxime, Hepatocellular-Cholestatic Hepatitis, Pancytopenia, Differential Diagnoses

1. Case Report

Drug-induced liver injury, although rare, is well studied. However, it often poses a diagnostic problem. Most cases of drug-related hepatotoxicity are due to antimicrobial drugs. With the following casuistry we would like to draw attention to this problem.

Patient's History: only child. Father: hay fever, mother: hypertension, history of recurrent pseudocroup and urinary tract infections in infancy with no evidence of vesicoureteral reflux. Allergies: grass pollen and dog hair; vaccinations up to date; no drug abuse.

History of presenting complaint: the patient fell ill 4 days before hospitalisation with a fever up to 39.6˚C, a dry cough and a sore throat. After 3 days of persisting fever cefuroxime axetil was prescribed. After the second dose an itchy rash developed on the whole body. The patient was admitted to hospital with "suspected sinusitis" and a "rash of unknown origin".

Clinical findings: 15-year old severely ill girl in poor general condition: throat and tonsils slightly red, no deposits; fine, itchy, partially confluent rash on the entire body.

***Laboratory findings* (*SI units*)**: are shown in Table 1: C-reactive protein 45.9; procalciton in 0.5; WBC 2.5; platelets 118; glucose, electrolytes, creatinine, urea and lactate within normal range; urine findings normal; iron 7.7 (4.1 - 2.9.9); transferrin 3.24 (2.0 - 3.1); transferrin saturation 9 (16 - 45); ferritin 1644 (13 - 150), ceruloplasmin, and alpha1-antitrypsin within normal range.

Coagulation diagnostics: Quick's value, INR, PTT, fibrinogen and thrombin time within normal range; elevated d-dimer 5.68 (<0.5).

Table 1. Laboratory findings over the course of hospitalization.

Parameter/ Day of treatment	Normal range (SI)	1st	2nd	3rd	7th	10th	23rd
CRP	0.1 - 3.3	45.9	27.8	22.9	7.4		
PCT	<0.5	0.5					
Hemoglobin	7.5 - 8.7	8.0	7.1	7.1	6.1	7.3	7.7
Hematocrit	0.37 - 0.47	0.36	0.33	0.34	0.28	0.35	0.36
WBC	3.8 - 9.8	2.5	1.9	2.1	3.9	7.1	
Neutrophils*	30 - 70	55.83	66.94	63.92	43.45	54.79	50.16
Neutrophilic staff cells†	0 - 11	44			16	14	
Segmented neutrophils†	36 - 84	32			32	34	
Platelets	150 - 300	117.6	100.8	111.4	338.1	669.4	
D-dimer	0 - 0.5	5.68			2.04		
ALT	0.2 - 0.6	4.88	3.46	4.05	2.72	1.82	0.48
AST	0.2 - 0.6	3.66	2.66	3.89	1.47	0.82	0.35
GGT	0.08 - 0.92	4.45	3.7	3.73	3.85	2.73	0.98
LDH	1.35 - 9.91	7.39	6.45		6.13	4.83	2.65
GLDH	<80	393			396	125	
Total Bilirubin	2 - 17	58.6		52.4	15.2	15.2	
Direct Bilirubin	0.1 - 5.0	50.1		44.2	10.6	11.4	
ALP	0.6 - 1.85	4.42	3.76		5.14	4.23	
Albumin	34 - 50	24.9		22.2	31.4	38.8	
Ferritin	13 - 150	1644				504	78.3

*flow cytometry; †microscopic.

Alanine aminotransferase (ALT) 4.88 (0.2 - 0.6); aspartate aminotransferase (AST) 3.66 (0.2 - 0.6); γ-glutamyltransferase (GGT) 4.45 (0.08 - 0.92); lactate dehydrogenase (LDH) 7.39 (1.35 - 3.91); glutamate dehydrogenase (GLDH) 393 (<80); alkaline phosphatase (ALP) 4.42 (0.5 - 1.85); cholinesterase 61 (88 - 215); lipase 1.31 (1.22 - 6.55); total bilirubin 58.6 (2 - 17); direct bilirubin 50.1 (0.1 - 0.5); total serum protein 53.3 (64 - 82); albumin 24.9 (34 - 50); ceruloplasmin, $alpha_1$-antitrypsin and urine findings normal.

Microbiological diagnostics: Negative results of blood culture, rapid antigen group A streptococcus test, pertussis PCR (nasopharyngeal swab), infectious mononucleosis rapid test, respiratory viruses multiplex PCR (Influenza A-, Influenza B-, Corona-, Entero-, Parecho-, Parainfluenza-, Metapneumo-, Boca-, RS-, Adeno-, Rhinovirus, Mycoplasma) and Cytomegalovirus DNA. Serological tests for toxoplasmosis, leptospirosis, hantavirusinfection and viral hepatitis including hepatitis E negative. Anti-HAV antibody positive, indicates successful vaccination. Anti-Hbsantibody negative, indicates non-response to vaccination.

No evidence of autoantibodies: AMA (anti-mitochondrial ab), ANA (antinuclear ab), anti-MPO (anti-myeloperoxidase ab), anti-PR3 (anti-proteinase 3 ab), anti-LKM (ab against endoplasmic reticulum of the liver) and anti-SLK antibodies (soluble liver antigen).

No abnormal abdominal ultrasound findings apart from a slight hepatomegaly; Normal FINDINGS on echocardiography. Chest x-ray showed slightly thickened bronchial walls, otherwise inconspicuous.

For laboratory findings over the course of hospitalization see table.

Clinical course: Treatment was initially symptomatic. Due to both the patient's poor general condition with recurrent vomiting and paraclinical signs of bacterial infection (elevated CRP and neutrophil left shift) antibiotic therapy with cefuroxime was then continued intravenously. Additionally, clarithromycin therapy was started in view of the patient's persistent cough until exclusion of pertussis and mycoplasma infection. The rash already been detected on admission flared up again. In the further course of illness hypoalbuminemia with edemas developed and treatment with human albumin was initiated. After eliminating other causes of hepatitis, cefuroxime-induced hepatocellular-cholestatic hepatitis with pancytopenia was diagnosed and cefuroxime therapy was stopped. The patient recovered quickly, hepatomegaly improved. The patient was discharged on the 10^{th} day of hospital treatment fully recovered.

2. Discussion

2.1. Epidemiology

Liver injuryis rarely caused by drugs. Larger studies is launched on drug-induced liver injuryare scarce [1] [2] [3] [4] especially on antibiotic-related cases [5] [6] [7] [8] with mainly individual case reports being published.

Drugs are the cause of 11% to 14% of liver disease [1] [2] [5]. Whereas a total incidence of drug-induced hepatitis of 14 - 20 or 10 - 15 per 100,000 population

per year has been reported by Spangenberg [3] and Agraval *et al*. [9]. Incidence per 100.000 prescriptions varies depending on the antibiotic substance [8], although erythromycin is considered the classic cause of drug-induced liver injury [5]. Incidence per 100.000 prescriptions is higher for amoxicillin/clavulanic acid 9.9 compared to macrolides (3.6), tetracyclines (1.5) or penicillin (0.1 - 0.3). In currently used antibiotic substances, the risk of drug-induced liver injury is approximately triple the risk of formerly used antibiotics (OR 2.6 to 7.7), the highest risk being reported by Udo *et al*. [7] and Ferrajolo *et al*. [10] on cotrimoxazole (OR_{adj} 24.16) and ceftriaxone (OR_{adj} 26.70).

Many studies indicate an increase in acute liver injury associated with antibiotic therapy. Incidence rates as high as 20 cases per 100,000 patients per year have been reported in the US [1].

Several studies from Wang *et al*. [4], Amin *et al*. [11], Ferrojolo *et al*. [10] and Molleston *et al*. [12] and have examined drug-induced liver injury in children. According to Amin *et al*. [11], drug-induced hepatitis accounts for 20% of cases of liver injury making it the majorcause of liver transplantation in the US. In a European case-control study, Ferrajolo *et al*. [10] identified 938 cases of hepatotoxicity in under 18 s with 93.665 controlls**.** Out of all 938 patients, 9.4% were under 2 years old, 10.8% were 2 - 5 years old, 27.8% were 6 - 11 years old, and 52.1% were 12 - 18 years old, ranging from 0.3 to 14 years, the mean age being 8.8 ± 3.9 years. No significant difference in gender was detected [4] [10]. Molleston *et al*., however, reported on 70% of patients being female [11].

2.2. Pathogenesis

The pathogeneticbasis of drug-induced hepatotoxicity caused by analgesics, antirheumatics, anticonvulsants etc., but mainly by anti-infectives, is an allergic or idiosyncratic reaction [2] [3] [4] [5] [6]. Wang found antimibrobial drugs to be responsible for 41.9% of cases of drug-induced liver injury, followed by herbal (29%) and antipyretic drugs (19.4%) [4]. Among antimicrobial drugs, beta-lactams, tetracyclines, macrolides, quinolones and sulfonamides are the types mainly responsible [5] [6] [13]. Drug-induced hepatotoxicity may present as hepatocellular (25.8%/78% of cases), cholestatic (25.8%/13%) or hepatocellular-cholestatic liver damage (48.8%/9%) [4] [11]. Drug-induced hepatotoxicity may, however, also present like an autoimmune reaction. Autoimmune diseases are therefore important differentials and should be excluded [5] [14].

2.3. Clinical Manifestations and Diagnostics

Patients with drug-induced liver injury may present with malaise, fever esp. ifundulatory (79%), loss of appetite, nausea, vomiting, upper abdominal pain, icterus (79%) or scleral icterus, pruritus (64%) associated with maculopapular rash [5] [9] [12] [15] [16] [17] [18]. The following paraclinical signs are indicative of cholestatic-toxic hepatitis: elevation of all liver enzymes, bilirubin including direct bilirubin, and alkaline phosphatise [10] [12] [15] [16] [17]. These

symptoms and signs were also observed in our patient.

Whereas an association with leukocytopenia and thrombocytopenia has been reported [19], anemia has not been noted before. The liver injury in our patient also caused an elevation of ferritin, but ferritin levels returned to normal after cefuroxime therapy was stopped.

The task of the attending clinician is to test for all relevant differential diagnoses. The following paraclinical parameters should be considered: liver enzymes, bilirubin and direct bilirubin, full blood count and differential blood count, coagulation diagnostics, laboratory tests for viral hepatitis, cytomegalovirus, Epstein-Barr virus and herpes simplex virus infection and for autoimmune hepatitis [5] [9] [16].

2.4. Cephalosporin-Induced Hepatitis

In our patient, cefuroxime therapy was found to be the cause of illness.

Antibiotic treatment with cefuroxime was initiated on the 4th day of fever as the clinical presentation indicated bacterial infection. Following only 2 doses of cefuroxime, an itchy rash developed on the whole body.

Drug-induced liver injury (DILI) is rarely caused by cephalosporins. In prospective studies, cephalosporins were found to be responsible for 4 out of 461 DILI cases (0.9%) in Spain, 1 out of 77 DILI cases (1.2%) in Sweden and 1 out of 96 DILI cases (1%) in Iceland. In the US, cephalosporins were more frequently responsible for drug-induced liver injury, with first-generation cephalosporins being the most common cause. Out of 33 cases of cephalosporin-induced liver injury, 19 were caused by cefazolin and 14 by other cephalosporins (5 cases due to 1st generation cephalosporins, 2 due to 2nd, 6 due to 3rd and 1 case due to 4th generation cephalosporin) [17]. Several reports on liver injury caused by first-generation [6] [17] [19] second-generation [14] and third-generation cephalosporins [15] [16] [18] [20] have been published. In our patient, both history and clinical findings lead to the diagnosis of cefuroxime-induced hepatocellular-cholestatic hepatitis.

2.5. Diagnoses, Antibiotics

Chen *et al*. [16] report on a case of hepatitisdue to cefdinir (3rd-generation cephalosporin) treatment for streptococcal pharyngitis. They point out that broad-spectrum antibiotics are too frequently used without sufficient indication.

Several similar cases have been reported: tonsillitis-ceftriaxone [15], Tonsillopharyngitis-cefprozil (3rd-generation cephalosporin) [20] upper respiratory tract infection-cefixime [18]. The reported side-effects in these cases could have been prevented as the antimicrobial spectrum of cephalosporins is unnecessarily broad for respiratory infections, tonsillitis and streptococcal pharyngitis [16].

2.6. Clinical Course and Treatment

Drug-induced hepatitis is a diagnosis of exclusion. The causative drug should

immediately be discontinued [8]. Additional symptomatic treatment with cholestyramine and corticosteroids has been described [9] [15] [16]. The latent period from ingestion of the causative drug untilclinical manifestation may last a few days up to several weeks [16] [17]. In our patient, latency until manifestation of clinical signs and paraclinical abnormalities was only a few days. Drug-induced liver injury has been reported subsequently to antibiotic courses of several days as well as single-dose antibiotic treatments; subsequent to oral as well as intravenous administration [17] [18] [19].

While bilirubin and liver enzyme levels in our patient returned to normal in the 4th week of illness, this may take up to 50 - 70 days after stopping the causative drug [16]. The mean duration of treatment is 25 days [4]. According to Chen *et al*. [16], all paraclinical parameters returned to normal within 77 days. However, persistentliver injury has been reported in 7% of cases with biopsies showing chronic hepatitis or impaired bile duct function [12].

2.7. Prognosis

The prognosis of liver injury caused by antibiotics is generally benign [4] [6] [8]. In a study of 30 children, the course of illness was rated as mild in 32%, moderate in 44% and severe in 20% of cases. The outcome was fatal in 4% of cases [12]. In a study on cefazolin-induced liver damage, 2 out of 19 patients with single-dose antibiotic treatments died [17]. Hussaini states that the risk of death and/or need of liver transplantation in patients with liver-injury in association with antibiotic treatment who develop icterus is about 10% [2] [6].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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