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BUDD-CHIARI SYNDROME WITH ACUTE LIVER FAILURE IN A 17 YEAR OLD PATIENT WITH SEPSIS DUE TO ACUTE SINUSITIS AND TREATMENT WITH AMOXICILLIN/CLAVULANATE

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ABSTRACT

Amoxicillin/clavulanate is a well known reason for causing an acute drug induced liver injury. Presentation and trend of the acute liver injury can differ in each individual: Cessation of drug use can lead to normalisation of liver function on the one hand, but also the necessity of liver transplantation or death due to acute liver failure are described in literature. Many reasons can lead to an acute Budd Chiari syndrome. Sepsis and other infectious diseases are discussed to be the second main cause after myeloproliferative diseases for abdominal thrombembolism and Budd Chiari syndrome. We present a 17 years old boy without any known liver disease with an acute liver failure after the use of amoxicillin/clavulanate for an acute sinusitis. After admission to our hospital for acute liver failure abdominal ultrasound and CT scan showed a portal vein and a liver vein thrombosis convenient for a Budd Chiari syndrome. In a CT scan of the neurocranium an acute sinusitis with the indication for a surgical treatment was verified. Liver biopsy showed an acute liver impairment with confluent necrosis. The histopathological presentation was consistent to a septic liver failure with a Budd Chiari syndrome and toxic second hit by amoxicillin/clavulanate. After administration of a therapeutic anticoagulation no more signs of portal vein and liver vein thrombosis were detectable. Full recovery of the health status was achieved three weeks after admission to our hospital.

Key words: Amoxicillin-clavulanate, Acute liver failure, Budd Chiari syndrome, Sepsis, Case report.

INTRODUCTION

Through different medical societies several definitions of an acute liver injury exist. According to King's College criteria acute liver injury is distinguished into a paracetamol and a non paracetamol induced liver injury. Acute non paracetamol induced acute liver injury is defined through an INR <6.5 on the one hand or through three criteria out of the following five criteria: Patient age < 10years or >40 years, Bilirubin > 17.4 mg/dl, INR >3.5, hepatic encephalopathy more than 7 days after jaundice onset or a non hepatitis A-E, Halotan or idiosyncratic genesis. In terms of Clichy criteria acute liver injury is characterised by an acute viral genesis with a hepatic encephalopathy II-III and a factor V < 30% in patients elderly than 30 years or a factor V < 20% in patients younger 30 years. Many different reasons can cause acute liver failure in adults as well as in paediatric patients.

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Beside viral infections, alcoholic hepatitis, different auto-immune syndromes, ischemic hepatopathy, malignant infiltration of the portal vein and many different drugs, the Budd Chiari syndrome is discussed to cause acute liver failure.

Budd-Chiari syndrome is defined as hepatic venous outflow tract obstruction, independent of the level or mechanism of obstruction, provided the obstruction is not due to cardiac disease, pericardial disease, or sinusoidal obstruction syndrome (veno-occlusive disease) [1]. Budd Chiari syndrome is considered primary when obstruction is because of an endoluminal lesion (thrombosis/web) and secondary when obstruction originates from a lesion outside the venous system (tumor, abscess, etc.) [2].

Antimicrobial drugs including antituberculosis agents are the most common cause of idiosyncratic drug-induced liver injury (DILI) and drug-induced acute liver failure worldwide [3]. Some antibiotics such as amoxicillin/clavulanate, isoniazid , moxifloxacine, as well as co-trimoxazole and flucloxacillin consistently top the lists of agents in retrospective and prospective DILI databases. Amoxicillin/ clavulanate is the leading cause of hospitalization from DILI in Spain [4-6].

Central nervous system agents, particularly antiepileptics, account for the second most common class of agents implicated in DILI registries. Antidepressants and non-steroidal anti-inflammatory drugs carry very low risk of significant liver injury, but their common use make them important causes of DILI [4]. Acute DILI is rare complication with an estimated incidence of 2.4-14.8 cases/ 100,000 person years [5]. The clinical presentation of DILI may vary, ranging from asymptomatic elevation of liver enzymes to progressive cholestatic liver failure. There are no clear insights into the pathogenesis of DILI at present. Genetic and environmental factors as well as immunologic factors are discussed [7-8].

Case Report

A 17 year old boy without any known or familiar liver injuries or other kinds of illnesses was transferred to the internal intensive care unit at the hospital of the University of Regensburg with an acute liver failure and a newly diagnosed portal vein and liver vein thrombosis in a CT-scan. Because of a severe sinusitis the patient was treated in a district hospital with amoxicillin/ clavulanate for 4 days. The medical history revealed no use or abuse of alcohol, drugs or any kind of long-term medication

In the initial analysis the laboratory parameters showed an acute liver failure with failure of coagulation (INR 2,98, Bilirubin 1,4 mg/dl, GOT 440 U/l, GPT 352 U/l, CHE 5063 U/l, albumin 21,4 g/l, factor V 21 %, factor VII 12 %). The transabdominal ultrasound indicated a portal vein thrombosis as well as an accentuated gall bladder. The liver veins were barred in the initial CT scan as well as in the initial transabdominal ultrasound, so that an acute Budd Chiari syndrome was diagnosed. In a repeated CT-scan one day after the initial CT scan to show any kind of progression of the thrombembolism, the portal vein thrombosis and the liver vein thrombosis were no longer detectable after the patient received a high dose of unfractionated heparin. Given that our patient was initially treated because of an acute sinusitis by the general practitioner and by soaring hepatic encephalopathy a CT scan of the neurocranium was administered. In this CT a severe sinusitis with indication for operative intervention was verified. No other morphologic reason for the confusion was detected via the CT scan. To drain the sinusitis by a septic patient and for the prevention of an intracerebral abscess a surgical treatment was performed.
As cause for the acute liver failure we were able to rule out viral infections, autoimmune liver disease, acute Wilson's disease. Also a bone marrow biopsy gave no evidence for a lymphoma. An antibiotic therapy with piperacillin and tazobactam was started and early escalated to meropenem, vancomycin and fluconazol. In short-term trend the hepatic encephalopathy rapidly aggravated within hours and the laboratory diagnostics showed a rapid impairment of liver function (GOT 2256 U/l, GPT 1775 U/l, INR 3,27, bilirubin 1,2 mg/dl, factor II 36 %, factor V 26 %). Intubation and pressure-controlled ventilation had to be performed one day after admission to our intensive care unit.

Due to rising lactate levels and increasing intraabdominal pressure an explorative laparatomia had to be performed. It showed an oedematous gall bladder and a regular liver perfusion (macroscopic and by intraoperative ultrasound).

In the hours after operative intervention of the sinusitis the patient developed a severe sepsis with a severe lactic acidosis (lactate 114 mg/dl)and the necessity of one-time renal dialysis. A vasopressive an inotropic therapy with norepinephrine 2,5 mg/h and epinephine 0,2 mg/h was necessary. By antibiotic therapy, large volume infusion and therapeutic anticoagulation the clinical situation and the liver function slowly improved and the infectious parameters declined.

Liver biopsy (taken during explorative laparatomia) showed an acute liver impairment with confluent necrosis. The histopathological presentation was consistent to a septic liver failure with a secondary Budd Chiari syndrome and toxic second hit by amoxicillin/ clavulanate.After five days after intubation the patient was trouble-free extubated. He showed no more signs of hepatic encephalopathy.

14 days after the first operative intervention it came to a mechanical ileus caused by adhesions, which was cured by surgery. Full resolution of the health status was achieved three weeks after the onset of the acute liver failure. The patient was dismissed home in excellent medical conditions. He was not involved in any clinical trial.

DISCUSSION

As shown in the introduction, many different reasons are known to cause an acute liver failure. In our case there are also different reasons which could have induced the acute liver failure although the incidence of idiopathic DILI in paediatric patients is relatively low and comparable with adults [3]. First of all in our case there is the paranasal sinusitis which leads to a sepsis in our patient. The reasons for the severe trend of the septic shock in our patient remain concealed. Any kind of immunudefiency as well as a HIV infection have been excluded.

In general Sepsis is beside cardiac and respiratory failures one of the most underlying condition for hypoxic hepatitis in intensive care patients [9]. Hypoxic hepatitis is characterised by a massive but transient rise in serum aminotransferases caused by anoxic necrosis of centrilobular liver cells. In this case we measured highly increased liver enzymes by entry which normalised during the intensive care treatment, so that a hypoxic hepatitis is possible in our patient.

Secondly a Budd Chiari syndrome was proven through an initial transabdominal ultrasound and CT-scan in our patient. Many different reasons are discussed to cause an acute abdominal vein thrombosis like a Budd Chiari syndrome. Aside from malignancies and myeloproliferartive disorders, other hypercoaguable states or infections are discussed to lead to an acute abdominal vein thrombosis. Dutta et al., estimated infections and sepsis as second important reason for abdominal thrombosis next to myeloproliferative disorders [10]. There are many publications reviewing abdominal thrombosis in septic conditions. Especially in pyelonephritis, diverticulitis and M. Crohn abdominal vein thrombosis and Budd Chiari syndrome in detail are known [11-13]. Two etiological ways are discussed to lead to an abdominal thrombosis therefore: During infection and sepsis it might be mediated via thrombogenic factors in the setting of inflammation on the one hand and/ or bacterial invasion on the other hand [14].

By bone marrow punction a myeloproliferative disorder and other hypercoaguable states like Factor V Leiden mutation etc. have been excluded in our patient. Furthermore in the peripheral blood count were no signs for a myeloproliferative disorder. In all imaging techniques there were no signs for a tumor in our patient. In conclusion we estimated therefore an infective reason for the Budd Chiari syndrome in our patient through the underlying sepsis. After beginning an anticoagulation there were no more signs of a Budd Chiari syndrome in the control CT-scan.

Thirdly different antibiotic agents have been used in our case. Initially amoxicillin/clavulanate was used for 4 days until to the transfer to our hospital. Amoxicillin/clavulanate and other antibiotic agents are well known reasons for an acute liver failure. In synopsis with the chronological administration of the different antibiotic agents we suppose amoxicillin/clavulanate as reason for the acute liver injury, because it was the only antibiotic agent which was used before the acute liver injury was diagnosed. Different trends of the liver failure after use of amoxicillin/clavulanate are described in literature. On the one hand a manifest acute liver failure with the necessity of a liver transplantation is described, even after antibiotic use [15]. Other authors describe a DILI after use of amoxicillin/clavulanate till to six week after completion the pharmacotherapy with a reversible liver damage [16]. In most instances respiratory tract infection and sinusitis were treated by amoxicillin/clavulanate with mean treatment duration of 13.9 days and a reaction time until first onset of jaundice and elevated liver enzymes of 25.2 days average after beginning the pharmacotherapy. Normalisation of liver enzymes was achieved around 11.5 weeks after cessation the drug therapy [17].

The highest relative risk of an acute DILI is associated with the use of more antibiotic drugs [5]. The risk of DILI from a combined current exposure to nonsteroidal anti-inflammatory drugs and other hepatotoxic drugs was more than additive [18].
However, despite cessation of amoxicillin/clavulanate for more than 6 months chronic liver injury and liver cirrhosis are described of a Spanish hepatotoxicity register [19].

CONCLUSION

In synopsis of all results we consider the acute liver failure of our young patient as an interaction of a septic liver shock by the acute paranasal sinusitis, a septic acute Budd Chiari syndrome and an idiosyncratic DILI through amoxicillin.

CONTRIBUTION

These authors equally contributed to this work.

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CONFLICT OF INTEREST:
The authors declare that they have no conflict of interest.

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