CASE REPORT

Favourable long term effect of ursodeoxycholic acid treatment on congenital vanishing bile duct syndromes

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Introduction

Vanishing bile duct syndromes (VBDS) constitute a heterogeneous group of diseases characterized by progressive disappearance of intrahepatic interlobular bile ductules (1). Several conditions have been related with VBDS, both congenital and acquired. Congenital abnormalities include Alagille syndrome, cystic fibrosis, a1 antitrypsin deficiency and progressive familial intrahepatic cholestasis (PFIC), while infections and medications can also cause VBDS later in life (2, 3). PFIC is a group of autosomal recessive disorders of bile formation that present with cholestasis, itching and jaundice (4).

Congenital VBDS lead to chronic cholestasis, development of cirrhosis and death from liver failure (2, 3). Primary biliary cirrhosis (or primary biliary cholangiopathy as has been recently renamed) is probably the best known example of these entities where both inherited and environmental factors are implicated (2). Ursodeoxycholic acid (UDCA) is a hydrophilic dihydroxy bile acid and is recommended for patients with primary biliary cirrhosis (5). Also, UDCA can be used as a treatment for other cholestatic syndromes due to its anticholestatic effects (5). In this article, we report a favorable long term effect of UDCA treatment in two patients with congenital vanishing bile duct syndromes. The first patient has been followed up in our clinic for the last 27 years whereas the second patient was first evaluated eight years ago.

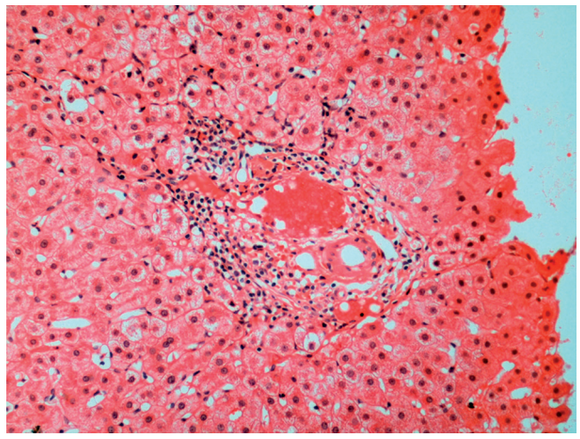

Figure 1.

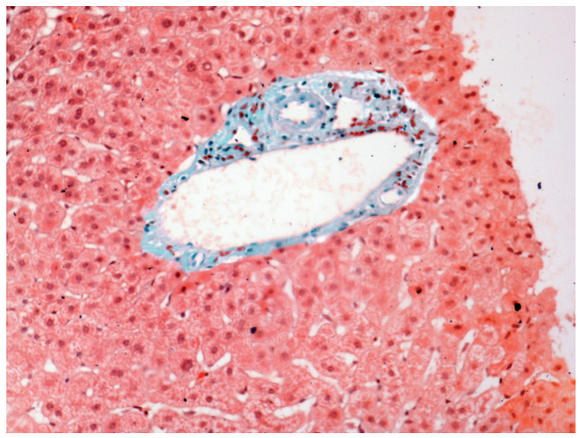

Figure 2.

Case 1

This female patient, today 41 years of age, experienced itching at the age of two and was treated and followed up by dermatologists. At the age of 14, liver biochemical tests were performed for the first time and revealed a cholestatic pattern (total bilirubin 1.8 mg/dl with four times the upper normal of both alkaline phosphatase and γGt values but only slightly elevated transaminases). The patient was referred to our outpatient clinic. Amenorrhea and facial features resembling Alagille syndrome were established. Pulmonary artery or vertebral abnormalities were not present. Liver biopsy revealed complete absence of small intrahepatic bile ducts (Figure 1). A diagnosis of incomplete Alagille syndrome was suggested but not genetically proved. Patient was commenced on UDCA at 16 years of age (15mg/Kg body weight) and after a period of six months alkaline phosphatase and γGt values dropped to near normal values and remained normal until today. After 6 years of treatment her menses appeared, whereas she remained slightly icteric. Repeated upper

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GI endoscopies over the years revealed no evidence of portal hypertension. At 34 years, still on the same dosage of UDCA, she became pregnant and had an uncomplicated labor. No features of Alagille syndrome were present in the baby. A second liver biopsy at that time showed absence of extensive fibrosis and only one small intrahepatic ductule in a portal tract (Figure 2). Total bilirubin at the time of biopsy was 2.5 mg/dl. The child, today 7 years old, is healthy with no evidence of cholestasis.

Case 2

A 29 years old patient today, presented with cholestatic biochemistry at birth. An extensive diagnostic investigation at the time ruled out metabolic causes and other congenital cholestatic diseases (cystic fibrosis, a1 antitrypsin deficiency, PFIC). At two months, a liver biopsy was performed and revealed cirrhosis with absence of intrahepatic bile ducts. A second liver biopsy at the age of 7 was also reported as cirrhotic with paucity of bile ductules. At the age of 21 she was first examined in our clinic. She was clinically well but amenorrhea, hypersplenism and cholestatic biochemistry were established. Upper GI endoscopy revealed portal gastropathy but absence of varices. Autoantibodies and viral markers were negative. An MRCP was negative for extrahepatic bile ducts and pancreatic ducts abnormalities. After 7 consecutive years on UDCA treatment (15mg/Kg body weight) her menses were restored. A new liver biopsy revealed regression of cirrhosis with an Ishak stage 4 fibrosis and abnormal, possibly newly formed bile ductules within fibrous septa (Figures 3 and 4).

Discussion

Vanishing bile duct syndromes and especially congenital VBDS are associated with high mortality from liver failure (2,3). VBDS, which belong to the heterogeneous entity of cholangiopathies (Table 1), include both congenital and secondary diseases which finally lead to cholestasis (6, 7).

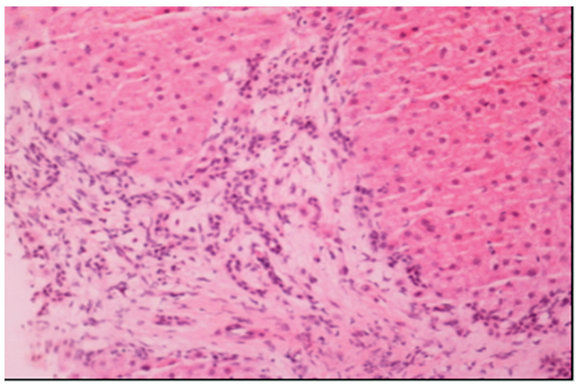

Figure 3.

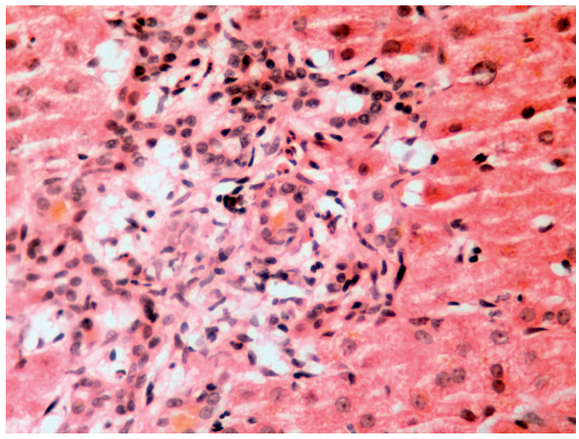

Figure 4.

Table 1. — **Cholangiopathies**[a]

Genetic and Idiopathic cholangiopathies	**Secondary cholangiopathies**
a1 antitrypsin deficiency	Abdominal trauma
Alagille syndrome	Chemical/Drugs
Autoimmune cholangitis	Iatrogenic biliary strictures
Bile duct/ Choledochal cysts	Infections/Sepsis
Biliary atresia	Vascular/Ischemic
Caroli syndrome	
Cystic fibrosis	
Idiopathic ductopenia	
IgG4-associated cholangitis	
Polycystic liver disease	
Primary billary cholangitis	
Primary sclerosing cholangitis	
Progressive familial intrahepatic cholestasis	

[a] Part of the data presented in Table 1 are adapted from reference 23.

Our study is the first report of favorable clinical and histological outcome after a long term treatment with UDCA of an otherwise lethal congenital condition. Interestingly, our first case had no cirrhosis after many years of mild cholestasis despite the persistent lack of intrahepatic bile ductules. We cannot explain this unexpected finding.

UDCA is a hydrophilic dihydroxy bile acid, initially used for gallstone dissolution (8). Hydrophobic bile acids in serum and bile are decreased with an increase in UDCA concentration up to 50% of the circulating bile acid pool (9). Several mechanisms of action of UDCA have been proposed. UDCA facilitates the fecal elimination of toxic bile acids (9) and the secretion of bile acids into bile by promoting activation of two bile acid carriers (the bile salt export pump BSEP and the conjugate export pump, MRP2) into the hepatocyte canalicular membrane (9). UDCA also reduces hepatocyte apoptosis induced by toxic bile acids (10) and increases the hepatocyte defense

mechanisms against oxidative stress (11). Moreover, UDCA modulates caspase activation and apoptosis in a concentration-dependent manner (12) and also modifies TLR4 and TLR9 signaling pathways, reducing inflammation (13).

Ursodeoxycholic acid is used in cholestatic conditions with a possible exception of primary sclerosing cholangitis (PSC), where the use of UDCA remains controversial (14). The European Association for the Study of the Liver (EASL) guidelines do not include a recommendation for the general use of UDCA in PSC (15), whereas the American Association for the Study of Liver Diseases does not recommend the use of UDCA in PSC (16). On the other hand, there are reports of UDCA administration in progressive familial intrahepatic cholestasis (PFIC) and Alagille syndrome. In these studies, UDCA treatment resulted in normalization of liver function tests, amelioration of pruritus and decrease of hepatosplenomegaly with simultaneous reduction in fibrosis (17,18). Amelioration of pruritus has also been reported in a study of 24 patients with congenital intrahepatic cholestasis, but follow up liver biopsies revealed no improvement of fibrosis (19).

Alagille syndrome is an inherited autosomal dominant disease, affecting multiple systems. It usually presents with cholestasis, due to hypoplasia of intrahepatic bile ducts, cardiac, facial and skeletal malformations. Liver failure complicates 20-30% of patients but only 10% undergo liver transplantation at a mean age of 30 years (20). The first patient had two of the five classical criteria described by Alagille et al for establishing the diagnosis (21). Although no gene testing for JAG-1 or NOTCH-2 was available, we believe that the most probable diagnosis was that of an incomplete variety of Alagille syndrome. Revision of pathology findings by an expert liver pathologist also confirmed our hypothesis.

Few cases of successful pregnancies in Alagille syndrome have been described (22) and only two reported the condition of the children after one year of life. One baby died at 3 months and the other was apparently normal. Our study also adds a case of a successful pregnancy in incomplete Alagille syndrome. The baby was born with normal labor and today, 7 years old, remains healthy without biochemical or clinical features of cholestasis.

The exact aetiology of the congenital cholestatic syndrome of the second patient is not known despite extensive investigation. Nonetheless, she also had a favorable clinical, biochemical and histological response after prolonged administration of UDCA confirming that congenital VBDS are an indication for UDCA treatment. It should be noted that amenorrhea, a common abnormality in VBDS, was restored in both patients after UDCA administration.

In conclusion, UDCA may be an efficacious alternative for the management of the rare cases of congenital vanishing bile duct syndromes.

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References

1. DESMET VJ. Vanishing bile duct syndrome in drug-induced liver disease. *J. Hepatol*., 1997, **26** : 31-5.
2. REAU NS, JENSEN DM. Vanishing bile duct syndrome. *Clin. Liver Dis*., 2008, **12** : 203-17.
3. NGUYEN KD, SUNDARAM V, AYOUB WS. Atypical causes of cholestasis *World J. Gastroenterol*., 2014, **20** : 9418-9426
4. JACQUEMIN E. Progressive familial intrahepatic cholestasis. *Clin. Res. Hepato. Gastroenterol*., 2012, **36** : 26-35.
5. CHAZOUILLÈRES O. Novel Aspects in the Management of Cholestatic Liver Diseases. *Dig. Dis*., 2016, **34** : 340-6
6. HOERNING A, RAUB S, DECHÊNE A, BROSCH MN, KATHEMANN S, HOYER PF, GERNER P**.** Diversity of disorders causing neonatal cholestasis-the experience of a tertiary pediatric center in Germany. *Front Pediatr*.**,** 2014, **2** : 65
7. GÖTZE T, BLESSING H, GRILLHÖSL C, GERNER P, HOERNING A. Neonatal Cholestasis - Differential Diagnoses, Current Diagnostic Procedures, and Treatment. *Front Pediatr.*, 2015, **3** : 43.
8. RUBIN RA, KOWALSKI TE, KHANDELWAL M, MALET PF. Ursodiol for hepatobiliary disorders. *Ann. Intern. Med.*, 1994, **121** : 207-18.
9. POUPON RE, CHRETIEN Y, POUPON R, PAUMGARTNER G. Serum bile acids in primary biliary cirrhosis : effect of ursodeoxycholic acid therapy. *Hepatology*, 1993, **17** : 599-604.
10. MARTEAU P, CHAZOUILLERES O, MYARA A, JIAN R, RAMBAUD JC, POUPON R. Effect of chronic administration of ursodeoxycholic acid on the ileal absorption of endogenous bile acids in man. *Hepatology*, 1990, **12** : 1206-8.
11. ARISAWA S, ISHIDA K, KAMEYAMA N, UEYAMA J, HATTORI A, TATSUMI Y, HAYASHI H, YANO M, HAYASHI K, KATANO Y, GOTO H, TAKAGI K, WAKUSAWA S. Ursodeoxycholic acid induces glutathione synthesis through activation of PI3K/Akt pathway in HepG2 cells. *Biochem. Pharmacol.*, 2009, **77** : 858-866
12. TSAGARAKIS NJ, DRYGIANNAKIS I, BATISTAKIS AG, KOLIOS G, KOUROUMALIS EA. A concentration-dependent effect of ursodeoxycholate on apoptosis and caspases activities of HepG2 hepatocellular carcinoma cells. *Eur. J. Pharmacol*., 2010, **640** : 1-7
13. KOUROUMALIS E, Notas G Primary biliary cirrhosis : From bench to bedside. *World J. Gastrointest. Pharmacol. Ther*., 2015, **6** : 32-58
14. HIRSCHFIELD GM KARLSEN TH LINDOR KD ADAMS DH. Primary sclerosing cholangitis. *Lancet*, 2013, **382** : 1587-99
15. EASL Clinical Practice Guidelines : management of cholestatic liver diseases. *J. Hepatol*., 2009, **51** : 237-67.
16. CHAPMAN R, FEVERY J, KALLOO A., *et al*. Diagnosis and management of primary sclerosing cholangitis. *Hepatology*, 2010, **51** : 660-78.
17. SRIVASTAVA A. Progressive familial intrahepatic cholestasis. *J. Clin. Exp. Hepatol.*, 2014, **4** : 25-36.
18. JACQUEMIN E, HERMANS D, MYARA A, HABES D, DEBRAY D, HADCHOUEL M., *et al*. Ursodeoxycholic acid therapy in pediatric patients with progressive familial intrahepatic cholestasis. *Hepatology*, 1997, **25** : 519-23.
19. DINLER G, KOCAK N, YUCE A, GURAKAN F, OZEN H. Ursodeoxycholic acid therapy in children with cholestatic liver disease. *Turk. J. Ped*., 1999, **41** : 91-98
20. KAMATH BM, SCHWARZ KB, HADZIC N. Alagille syndrome and liver transplantation. *J .Ped. Gastroenterol. Nutr.*, 2010, **5** : 11-5.
21. ALAGILLE D, ESTRADA A, HADCHOUEL M, GAUTIER M, ODIÈVRE M, DOMMERGUES JP. Syndromic paucity of interlobular bile ducts (Alagille syndrome or arteriohepatic dysplasia) : review of 80 cases. *J. Pediatr.*, 1987, **110** : 195-200
22. FERRARESE A, SENZOLO M, BURRA P. Successful pregnancy in Alagille Syndrome. *Dig. Liver Dis*., 2015, **47** : 86-7.
23. LAZARIDIS KN, LARUSSO NF. The Cholangiopathies. *Mayo. Clin. Proc*., 2015, **90** : 791-800.