# Nonsydromic paucity of interlobuler bile ducts: Two children with a benign course

## Nonsendromatik interlobular safra kanalları azlığı: Benign gidişli iki çocuk olgu

Aydan KANSU MD[1], Tümay DOĞANCI MD[1], Esra ERDEN MD[2], Nurten GİRGİN MD[2]

*University of Ankara, School of Medicine, Department of Pediatric Gastroenterology[1] and Pathology[2], Ankara*

**SUMMARY:** *Paucity of interlobular bile ducts, which is defined as a reduction in the number of interlobular bile ducts, is a significant abnormality causing intrahepatic cholestasis in children.The nonsyndromic form which is seen rarely, may be idiopathic or associated with various specific clinical conditions. The syndromic form usually shows clinical improvment, while development of cirrhosis is common in the nonsyndromic form.*

*We describe two children with nonsyndromic paucity of interlobular bile ducts diagnosed in the neonatal period, in whom clinical and biochemical improvement occurred in about six months.*

**Key words:** Paucity of interlobular bile ducts, childhood

**ÖZET:** *Karaciğer portal alanında interlobuler safra duktusları sayısında azlık ya da yokluk olarak tanımlanan interlobuler safra kanalları azlığı, çocuklarda intrahepatik kolestaza neden olan önemli bir anomalidir.Nadir görülen nonsendromatik formu bazı spesifik klinik bulgularla birlikte olabileceği gibi idiyopatikde olabilmektedir. Sendromatik formdaki hastalarda genellikle klinik olarak düzelme gözlenirken nonsendromatik formdaki hastalarda siroz gelişimi sıktır.*

*Burada yenidoğan döneminde kolestaz bulguları gösteren ve idyopatik nonsendromatik interlobüler safra kanalları azlığı tanısı alan ve tanıdan sonra yaklaşık altı ay içinde klinik ve biokimyasal düzelme gösteren iki olgu sunulmaktadır.*

**Anahtar sözcükler:** İnterlobuler safra kanalları azlığı, çocukluk

Interlobular bile duct paucity is defined as absence or marked reduction in the number of interlobular bile ducts within the portal tracts of the liver (1). The nonsyndromic form, which is less often seen than the syndromic form, commonly progresses to cirrhosis (2). We describe two children with idiopathic nonsyndromic interlobular bile duct paucity, in whom clinical and biochemical improvement occurred.

### Case 1

A two-month-old boy was referred to our department due to direct hyperbilirubinemia and acholic feces. Jaundice was present since birth. His parents were first degree relatives.At the time of referral, physical examınation revealed icterus and mild hepatomegaly, with normal physical development. Laboratory data included total bilirubin 6, 64 mg/dL, direct bilirubin 4, 18 mg/dL, AST 107 U/L, ALT 79 U/L, alkalin phosphatase 262 U/L (normal range: 145-420 U/L) and GGT 80 U/L. Total protein, albumin, prothrombin time and partial thromboplastin time were within normal limits.Abdominal ultrasound was normal.

Serologic investigations for HAV, HBV, HCV, toxoplasmosis, rubella, cytomegalovirus, herpes simplex, Epstein-Barr virus and syphilis were negative.Urine and serum aminoacids, alpha-1 antitrypsin level, urine for reducing substances and sweat test were normal hepatobiliary scan showed normal hepatic uptake but biliary excretion was absent. Liver biopsy was performed which showed cholestasis characterized by canalicular bile plugs (Figure 1). Four bile ducts were seen in 10 portal tracts (Ratio: 0.4). Radiologic investigation for butterfly vertebra was negative, cardiac evaluatıon was unremarkable.

Idiopathic nonsyndromic interlobular bile duct paucity was diagnosed with these clinical and laboratory findings.The infant was breast feeding, he was supplemented with vitamin A, D, E, and K

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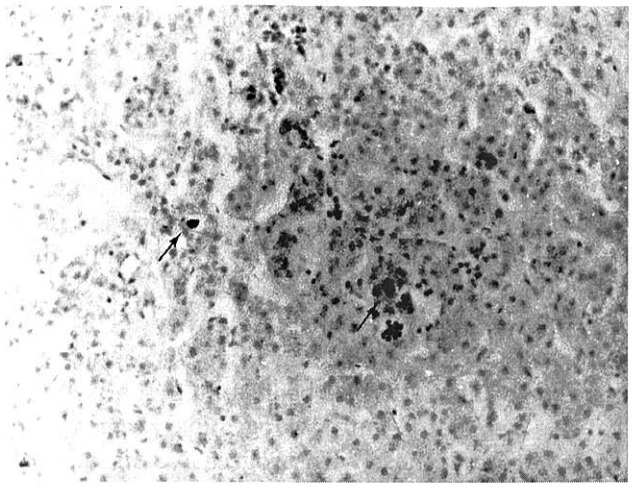

**Figure 1:** Initial liver biopsy of the case I, H-E, x200. There is cholestasis characterized by canalicular bile plugs and marked reduction in the number of interlobular bile ducts.

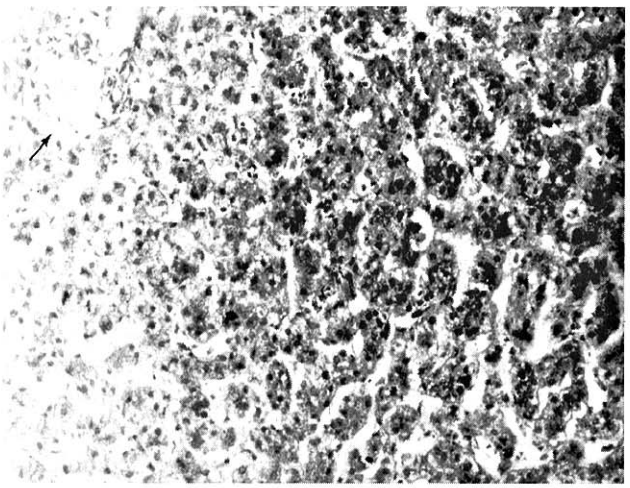

**Figure 2:** Second liver biopsy of case I, performed at age 2. Masson-Trichrom, x200. Cholestasis is resolved, but reduction in the number of interlobular bile ducts persists.

and ursodeoxycholic acid was started. During follow-up, he was in good health with normal physical development. Jaundice regressed, and by the age of six months his physical examination was normal, and biochemical tests were within normal limits. A second liver biopsy was performed at two years of age (Figure 2). There was no finding associated with cholestasis, but only 3 bile ducts were seen in 10 portal tracts (Ratio 0, 3).

He is now three years old with normal physical examination and normal laboratory values.

## Case II

A 20-days-old boy was hospitalised to evaluate direct hyperbilirubinemia, with jaundice and acholic feces evident since birth. He was the third living baby of first degree relative parents, his brother had thalassemia major and our patient was a thalassemia carrier.His physical examination showed icterus but was otherwise normal.

Laboratory data included total bilirubin 12 mg/dl, direct bilirubin 4, 24 mg/dl, AST 54 U/L, ALT 100 U/L, GGT 12 U/L. Total protein, albumin and prothrombin time were normal. Abdominal ultrasound was within normal limits. Serologic investigations for HAV, HBV, HCV, toxoplasmosis, rubella, cytomegalovirus, herpes simplex, Epstein Barr virus and syphilis were negative. Urine and serum aminoacids, alpha-1 antitrypsin level, urine for reducing substance and sweat test were normal. A hepatobiliary scan showed normal hepatic uptake but biliary excretion was absent. Liver biopsy was performed which showed chronic cholestasis with canalicular bile plugs.Two bile ducts were seen in 14 portal tracts (Ratio: 0.14). Radiologic investigation for buttefly vertebra was negative, cardiac evaluation was unremarkable.

Idiopathic nonsyndromic interlobular bile duct paucity was diagnosed on the basis of these clinical and laboratory findings.The infant was breast feeding; he was supplemented with vitamins A, D, E and K and ursodeoxycholic acid was started. During follow-up he remained well, his physical development was within normal limits. Jaundice regressed and physical examination as well as biochemical tests were normal when he was six months old. A second liver biopsy was performed at age 18 months which showed five bile ducts in 13 portal tracts (Ratio: 0.38). Canalicular bile plugs were not seen.

He is now three years old with normal physical examination and normal laboratory values.

## DISCUSSION

TInterlobular bile duct paucity, which is defined as absence or marked reduction in the number of interlobular bile ducts within the portal tracts of the liver, is a significant anomaly causing intra-

hepatic cholestasis in children. Histopathologically, it is expressed as the ratio of the number of interlobular bile ducts to the number of portal tracts and this ratio is between 0.9 and 1.8 in livers of normal children.Interlobular bile duct paucity should be suspected when this ratio is found to be below 0.9 (1). Although the etiopathogenesis is not clear, congenital absence of bile ducts, partial atrophy or a progressive reduction in the number of bile ducts have been suggested (1).

Clinically, bile duct pauticy in neonates can be either syndromic, which is called Alagille syndrome, or nonsyndromic. Alagille syndrome is characterised by a peculiar face, chronic cholestasis, posterior embryotoxon, butterfly-like vertebral arch defects and peripherial pulmonary artery hypoplasia or stenosis (3).

The non syndromic form of interlobular bile duct paucity can be associated with several clinical conditions such as alpha-1 antitrypsin deficiency, cystic fibrosis, graft-versus-host disease, liver transplant rejection, congenital infection with cytomegalovirüs and rubella, or chromosomal abnormalities.A clinical condition unassociated with these findings is accepted as idiopathic nonsyndromic bile duct pauticy (1).

That two patients presented here were admitted with findings and symptomatology of neonatal cholestasis. Cholestatic jaundice in infancy is an important clinical condition of multiple etiologies; neonatal hepatitis and extrahepatic biliary atresia are two main causes (4). Paucity of interlobular bile ducts is a rare cause of intrahepatic cholestasis.

Bile duct paucity can be defined only histologically, and requires a sufficiently large liver biopsy that contains at least five portal tracts (1).The diagnosis of our patients was based on histopathologic evaluation of the liver. Clinical features described in Allagille syndrome were not present in our cases, nor were there clinical conditions associated with bile duct paucity, which led us to a diagnosis of idiopathic nonsyndromic bile duct paucity. This is seen more rarely and there are only a few reports about this entity (5, 6). The prognosis of nonsyndromic bile duct paucity is highly variable. It has been stated the patients can be separated into two groups according to their outcome: those with progressive disease and those with a benign course (7). Progression to cirrhosis has been reported to occur in 45 % of patients.However this progression in patients with Alagille syndrome on the other hand is seen in only 14% of cases (8).

Clinical and biochemical resolution was seen very early in our patients, about six months after diagnosis. Berezin et al reported a neonate with nonsyndromic bile duct paucity in whom biochemical resolution occurred at 5 years of age (9). In this case, development of normal bile ducts was demonstrated histopathologicaly.

Repeat liver biopsies performed in our patients one year after clinical and biochemical resolution, showed the persistance of bile duct paucity. Our patients manifested nonsyndromic interlobuler bile duct paucity with immediate clinical and biochemical resolution but without histologic normalisation and demonstrate that the natural course of this clinical condition can be heterogenous and benign.

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