Fifteen years single center experience in the management of progressive familial intrahepatic cholestasis of infancy

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Abstract

Recent advances in genetics and in physiopathology of bile composition and excretion have clarified the understanding of progressive familial intrahepatic cholestasis (PFIC).

The aim of the present study is to review the experience of our center in terms of diagnosis, management and outcome of 49 pediatric PFIC patients, belonging to the three classical subtypes described.

We analyse the clinical, biological, and histological patterns and review the response to the medical and surgical treatment and the global outcome.

The only clinical difference between the different subtypes of PFIC patients was the intensity of pruritus. Serum gamma-glutamyltransferase (GGT) and liver histology allowed to differentiate PFIC III from PFIC I and II patients.

High levels of biliary bile acids in 2 low-GGT patients was associated with favourable outcome. Response to ursodesoxycholic acid (UDCA) varies from patient to patient and was not associated to a particular subtype of PFIC. In five patients of this cohort, external biliary diversion was performed without improvement.

Transplantation is indicated whenever medical treatment fails to restore normal social life, growth and well being of the child and it is associated with excellent survival (> 90%). (Acta gastroenterol. belg., **2004**, 67, **313-319**).

Key words : familial intrahepatic cholestasis, liver transplantation, Byler's disease, liver, cholestasis, ursochenodesoxycholic acid, biliary diversion.

Abbreviations : PFIC : progressive familial intahepatic cholestasis – OLT : orthotopic liver transplantation – PBD : partial biliary diversion – UDCA : ursodesoxycholic acid – GGT : g glutamyl-transpeptidase – ASAT : aspartate aminotransaminase – ALAT : alanine aminotransaminase – BRIC : benign recurrent intrahepatic cholestasis – ICP : intrahepatic cholestasis of pregnancy – CA : cholic acid – CDA : chenodeoxycholic acid.

Introduction

Progressive familial intrahepatic cholestasis (PFIC) is an heterogeneous group of autosomal recessive liver disorders of childhood. This disease occurs in infancy and results in progressive cholestasis and liver failure. The physiopathology has long remained unclear. Recent advances in genetics, molecular biology and bile composition analysis has partially solved this enigma. A new classification has been proposed to describe formerly called Byler disease and Byler syndrome (1,2,3,4) (table 1).

PFIC type I (also called Byler disease) is characterised by recurrent episodes of jaundice, pruritus, normal serum gamma-glutamyltransferase (GGT) and cholesterol levels, elevated concentration of serum primary bile acid and low concentration of biliary bile acid. The genetic defect (ATP8B1) is localised on chromosome 18q21-22 (5). This gene codes for a P-type ATPase, an ATP dependent membrane transporter which probably regulates the distribution of aminophospholipids (6,7). ATP8B1 is also responsible of the wild phenotype, benign recurrent intrahepatic cholestasis (BRIC) and the Greenland familial cholestasis (8,9). This transporter is expressed in many tissues which may explain the extrahepatic symptoms associed with PFIC1 (diarrhea).

Like PFIC 1, PFIC 2 is an autosomal recessive disease which induces pruritus, cholestasis, normal serum cholesterol levels and GGT, high serum biliary acid concentration and very low biliary bile acid concentration. The locus for PFIC2 is mapped on chromosome 2q24 (ABCB11 or BSEP) (10). This gene codes for the SPGP (sister of P-glycoprotein) also called bile salt export pump (BSEP) and which is expressed in the canalicular membrane of hepatocytes (11,12). The affected patients have a decreased biliary bile salt secretion with accumulation of bile salt in the hepatocyte causing severe cellular damage. PFIC 1 and 2 liver histology is characterised by cholestasis with absence of ductular proliferation.

PFIC 3 is due to a defect in the multidrug resistance 3 (MDR3) gene, which codes for a canalicular translocator of phosphatidylcholine (13,14,15). The disease is distinguished from the other types by a high serum GGT and ductular proliferation on liver histology. The heterozygous mutations have been found in women with intrahepatic cholestasis of pregnancy (ICP).

Few studies report the long term prognosis of these patients and especially prognosis related to clinical, biochemical, histological and genetic parameters. The aim of the present study is to review the experience of our center in terms of diagnosis, management and outcome in a population of 49 patients since the last 15 years, according to different treatment options including liver transplantation.

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Table 1. — **Subtypes and characteristics of progressive familial intrahepatic cholestasis**

	PFIC 1	PFIC 2	PFIC 3
Transmission	Autosomal recessive	Autosomal recessive	Autosomal recessive
Chromosomal locus	18 q21 (ATP8B1)	2q24 (ABCB11)	7q21 (ABCB4) (MDR3 expression)
Molecular change and function defect	Absence of P-type ATPase (FIC1) – distribution of aminophospholipids	Absence of ATP dependent bile acid transporter (BSEP = SPGP) – bile acid transport into bile	Absence of multidrug resistance 3P glycoproteinRNA (MDR3) – translocation of phosphatidylcholine into bile
Function defect location	– Hepatocyte canalicular membrane – Cholangiocyte – Large range of tissues	– Hepatocyte canalicular membrane	– Hepatocyte canalicular membrane
Phenotype	– Severe pruritus – Cholestasis – Chronic watery diarrhea – Liver failure	– Severe pruritus – Cholestasis – Liver failure	– Moderate pruritus – Portal hypertension
Serum GGT activity	Normal / low	Normal/ low	High
Histology	Canalicular cholestasis, fibrosis	Canalicular cholestasis, fibrosis	Ductular proliferation
Bile composition	Low bile acid concentration	Very low bile acid concentration	Low phospholipid concentration

Patients and methods

During the last 15 years, 49 patients suffering from PFIC were admitted for assessment and treatment in our Pediatric Hepatology Unit. All patients met the published criteria of PFIC including history of chronic cholestatic liver disease with jaundice, hepatomegaly and/or pruritus. The scale described by Whitington was used to appreciate the intensity of pruritus (0 = none ; 1+ = rubbing or mild scratching when undistracted ; 2+ = active scratching without evident skin abrasion ;3+ = abrasions evident, 4+ = cutaneous mutilation, hemorrhage, evident scarring) (16). Appropriate investigations were performed to exclude other etiologies of chronic cholestasis. Especially in cases of elevated GGT serum levels, sclerosing cholangitis was excluded by percutaneous cholangiography.

Two groups of patients were defined according to serum GGT levels : low GGT group when the serum level was below 55 IU/L and high GGT group including patients having GGT exceding 1.5 time the upper limit of normal. The two groups were compared for parameters such as age of first symptoms, pruritus, jaundice, hepatomegaly and liver function tests (Table 2).

Liver biopsy was performed and examined to evaluate the criteria published by Bull *et al.* (17). In the two groups of PFIC patients separated according to serum GGT levels, the following features were studied : cholestasis, giant cell transformation, degenerative changes of bile duct epithelium (ductular proliferation or ductular losss), fibrosis and cirrhosis (Table 3).

Primary bile salts in serum were measured by gas chromatography and mass spectrophotometry. Bile salts in urine were checked by fast-atom bombardment mass spectrophotometry to exclude primary bile acid synthetic defect. When bile was available, quantitative measurement of primary bile acids were performed . Genetic mutation analysis was performed whenever possible for PFIC II mutations (Table 4).

Twenty patients received medical treatment at diagnosis. The management of cholestasis in infants included high caloric formula enriched with branched chain amino acids and medium chained triglycerides, vitamins, minerals, treatment of complications such as ascites and oesophageal varices, and ursodesoxycholic acid (UDCA) at the dose of 30 to 45 mg/kg/day (18,19). Patients admitted during the time period of 1985-90 did not receive UDCA. Rifampicine was given at 10mg/kg/day in two divided doses to patients with intense pruritus (20). The response to UDCA was evaluated 6 and 12 months later with the clinical scores and liver function tests (Table 5).

Biliary drainage surgery was performed in 4 patients in the low-GGT group at the time of diagnosis (16,21). One patient in the high-GGT group had undergone biliary drainage surgery elsewhere. Orthotopic liver transplant (OLT) was proposed immediately to 27 patients while 11 other patients were registered on the transplant list after failure of medical treatment. The follow-up survival of 38 PFIC patients who underwent liver transplant is compared to the survival in a cohort of 450 patients (less than 15 years old) who were trans-

Table 2. — **Clinical and biological presentation of PFIC patients**

	PFIC I & II n = 30/49 (61%)	PFIC III n = 19/49 (39%)	P
Sex	18 M / 12 F	8 M / 11 F	
Median age of apparition in months (range)	2 (0-58)	3 (0-36)	
Pruritus	23/24 (96%)	7/17 (41%)	*< 0,01*
Clinical jaundice	19/27 (70%)	14/17 (82%)	*NS*
Hepatomegaly	19/21 (90%)	13/17 (76%)	*NS*
Median ASAT (IU/L) (range) (N < 55)	172 (36-822)	132 (91-315)	
Median ALAT (IU/L) (range) (N < 40)	156 (22-746)	127 (44-853)	
Total / Direct bilirubin (mg/dl)	5,6 / 4,6	7,4 / 4,0	

NS : not significant.

This table reports the clinical and biological characteristics of 49 patients with PFIC, separated into low GGT (PFIC I & II) and high GGT patients (PFIC III).

Table 3. — **Histologic features of PFIC patients**

	PFIC I &II n = 25	PFIC III n = 14	P
Cholestasis	20 (80%)	8/14 (57%)	*NS*
Giant cell transformation	1 (4%)	1 (7%)	*NS*
Hepatic ductular loss	2 (8%)	2 (14%)	*NS*
Hepatic ductular proliferation	2 (8%)	7 (50%)	*< 0,02*
Hepatic fibrosis	15/ (60%)	10 (71%)	*NS*

Table 4. — **Biliary bile acid analysis**

	BILE C A (µ M/L)	 CD A (µ M/L)	MUTATION 2q24	OUTCOME
γ GT ↓ (n = 9)	22	0	+	OLT
	22	17	+	OLT
	7,7	0	+	OLT
	5	2	+	OLT
	0	0	+	PBD - OLT
	595	10	na	OLT
	199	18	–	a&w
	20805	10566	–	a&w
	38880	296	–	a&w
γ GT ↑ (n = 5)	185	3425		OLT
	12099	11839		a&w
	2541	8242		OLT
	15832	1017		a&w
	12951	20747		a&w

a&w : alive and well without transplantation
na : not available
OLT : orthotopic liver transplantation
PBD : partial biliary diversion

Bile concentrations of cholic acid (CA) and chenodesoxycholic acid (CDA) in 14 patients with PFIC. Mutation analysis was available in the low GGT group. All PFICII patients had very low levels of biliary bile acid excretion and required OLT.

planted for other chronic cholestatic diseases, mainly biliary atresia, in our center (Fig. 2). Global outcome according to the different managements is given in table 6 and fig. 3.

Results

Clinical, biological and histological parameters (Table 2 and 3)

Table 2 and 3 summarise the patients' characteristics. Pruritus and the ductular proliferation were the only parameters that differ significantly between the 2 groups, as detailed.

Bile analysis (Table 4)

Bile analysis was performed in 14 patients (9 from the low-GGT group and 5 from the high-GGT group). All 5 patients in the high-GGT group had normal bile acid concentrations. Otherwise, 7 out of 9 patients in the low-GGT group had low bile acid concentration in their bile. The 2 others low-GGT patients had high biliary bile acid concentration and both had favourable clinical

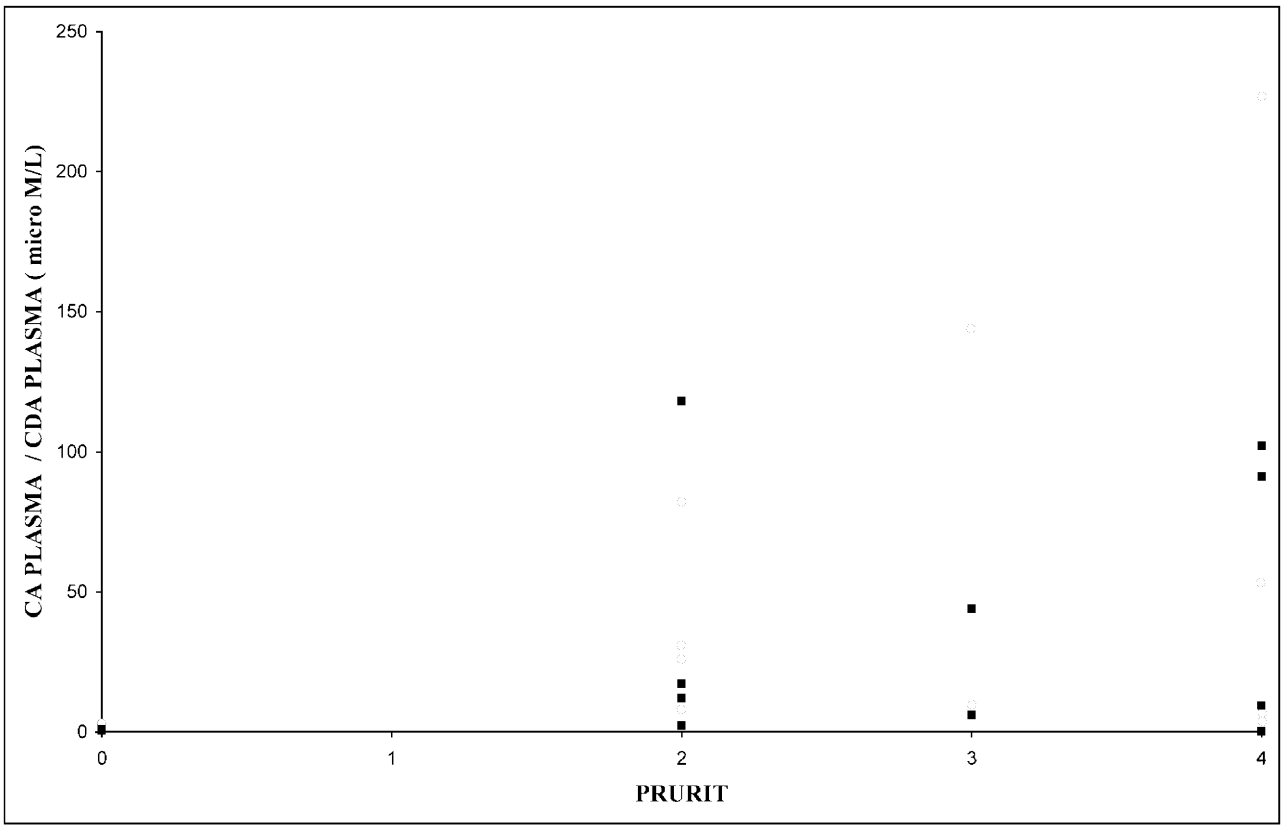

Fig. 1. — Pruritus correlated to plasma bile acids

■ : PLASMA CDA (µ M/L)
● : PLASMA CA (µ M/L)

Correlation of pruritus intensity and plasma bile acid concentration.

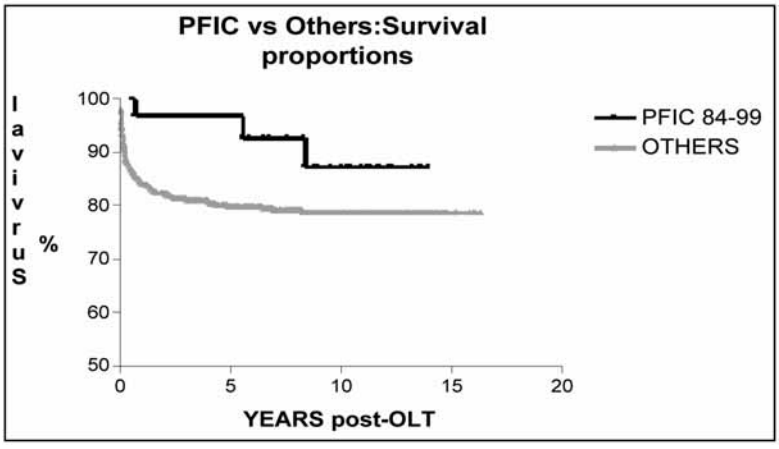

Fig. 2. — Long term survival after OLT

OTHERS = non PFIC OLT

Actuarial survival of 38 transplanted PFIC patients is compared to the cohort of 450 pediatric OLT patients transplanted during the same period for other chronic cholestatic disease.

Table 5. — **Response to UDCA (n = 20) (low GGT n = 11, high GGT n = 9)**

	TYPE	at diagnosis	6 months UDCA	12 months UDCA
FAVORABLE RESPONSE				
median ASAT (UI/L) (range)		101 (36-315)	43 (29-79)	35 (20-76)
median ALAT (UI/L) (range)	↓ γGT(n = 5)	112 (29-282)	40 (19-137)	30 (14-80)
median total bilirubin (mg/dl) (range)	↑ γGT(n = 5)	5 (0-8)	0,3 (0-2)	0,3 (0-3)
median direct bilirubin (mg/dl) (range)		3,6 (0-6)	0,1(0-1)	0,1 (0-2)
PARTIAL RESPONSE				
median ASAT (UI/L) (range)	↓ γGT(n = 6)	167 (100-810)	82 (58-182)	100 (45-254)
median ALAT (UI/L) (range)	↑ γGT (n = 4)	196 (65-613)	64 (49-199)	77 (36-256)
median total bilirubin (mg/dl) (range)		5,3 (1-32)	3,3 (0-6)	2 (0-35)
median direct bilirubin (mg/dl) (range)		4,4 (1-8)	2,6 (0-44)	1,4 (0-24)

Response to UDCA was equally observed in patients from both high and low GGT subtypes.

Table 6. — **Global outcome according to the PFIC subtypes**

	PFIC I &II n = 30/49 (61%)	PFIC III n = 19/49 (39%)	P
Response to UCDA	5/11 (45%)	5/9 (55%)	*NS*
OLT	22/30 (73%)	13/19 (68%)	*NS*
Median age of OLT in months (range)	50 (19-189)	63 (17-129)	
Median time diagnosis / OLT In months (range)	57 (18-188)	53 (16-124)	
Survival	27/30 (90%)	18/19 (95%)	*NS*

outcome, with mild to moderate persisting pruritus at the ages of 8 and 12 years.

PFIC II mutation was found in 5 patients in the low-GGT group. The bile analysis showed very low bile acid concentration in these patients. The intensity of pruritus tended to correlate with serum bile acid levels, as shown in figure 1, although not significantly (p = 0.5).

Response to medical and surgical treatment (Table 5 and 6)

In 27 patients, no attempt of medical treatment was made in view of advanced disease. They were immediately considered as candidate for OLT.

Twenty other patients received UDCA as soon as diagnosis was confirmed (Table 5). Ten patients (5 in each group) responded to medical treatment, with complete normalisation of liver enzymes and disappearance or marked improvement of pruritus. The 10 remaining medically treated patients (6 in the low-GGT group) had a partial response, with mild improvement of liver enzymes and persisting pruritus. Seven had OLT and 3 had external biliary drainage followed by OLT because of poor response (n = 2) or no response (n = 1) to biliary drainage.

Two additional patients underwent directly partial biliary diversion, without favorable outcome. One of them died from sepsis and massive fluid losses and the other was transplanted .

Finally 38 patients underwent OLT. One died from sepsis following surgery, one other from chronic aggressive post transplant hepatitis C and one from unknown cause when back in the native country. Overall survival rate 5 years after OLT is therefore 35/38 (92%) in this series. On the other hand the long term (5 years) survival rate of all children who underwent OLT is 78% for the same period in our unit (Fig. 2).

Survival rate in all of our 49 patients is 45/49 (92%). There was not significant difference in terms of response to the different treatments and survival between the PFIC subtypes (Table 6). Figure 3 summarises the management and outcome of all 49 PFIC patients.

Discussion

Recent articles have focused on specific biochemical or genetic aspects of PFIC from a large number of different centers. This study reports an overview of a large cohort of patients followed over a 15-year period in a single pediatric hepatology center.

Although it may be argued that the genetic testing should be obtained in all patients with PFIC, the reality is that these tests are performed only in certain specific centres which are flooded with demands. Therefore, it remains important for the clinician to classify patients using clinical and simple biochemical tests. Furthermore it would be very practical to anticipate prognosis on the basis of relatively accessible investigations.

As detailed in table 1, simple parameters such as intensity of pruritus, GGT serum level and histologic findings enable the clinician to differentiate PFIC III from PFIC I and II. Differentiating PFIC I from PFIC II patients requires advanced investigations such as BSEP immunostaining, or ideally genetic mutation analysis. Although described to have a more severe and rapid evo-

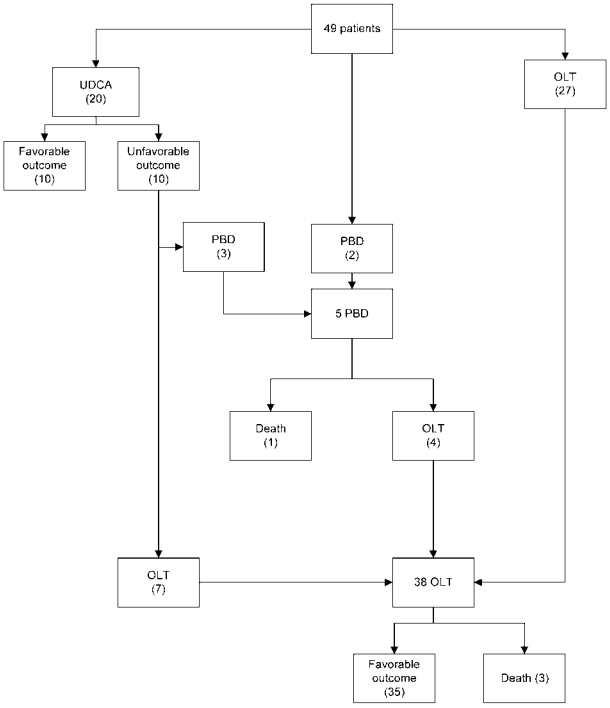

Fig. 3. — Overall series evolution according to the different managements

OLT : orthotopic liver transplantation
PBD : partial biliary diversion.

lution, the low GGT patients in our serie did not differ from the high GGT group in terms of age of first symptoms, severity of cholestasis, fibrosis and outcome (1,4) (Table 2, 6).

Pruritus seems to be correlated to a higher level of serum bile acid in low-GGT patients although no statistical differences was observed (Fig. 1). Moreover the defect of biliary excretion explained the trend to higher level of serum bile acids in low GGT patients.

Among the 9 low-GGT patients in whom bile analysis was performed, 5 had low biliary salts concentration and they did not respond to medical treatment. Lack of bile salt excretion in these patients has now been linked with absence of Bile Salt Export Pump and PFICII mutation, the specific ATP dependant bile salt transporter normally expressed at the canalicular membrane of hepatocytes (12).

However 2 low-GGT patients with pruritus had high levels of biliary bile acids. They had favourable outcome, without cirrhosis. They had a clearly different pattern of bile acid excretion differing from the PFICII phenotype. These patients had a milder clinical disease more suggestive of Benign Recurrent Intrahepatic Cholestasis (BRIC) whose mutation is reported to be an allele of PFIC I (8).

On the other hand, patients in the high-GGT group had less pruritus. Despite cirrhosis and cholestasis these patients had lower levels of serum circulating bile acids and higher biliary bile acid concentration. This indicates that low bile excretion in high GGT patient is not related to their cirrhosis or cholestasis.

Response to UDCA confirms previous observations about the importance of starting UDCA therapy as soon as the disease is suspected, and bile sampling performed (19). 50% of the patients treated with UDCA responded fully to treatment avoiding disease progression and OLT. In other patients the disease parameters were improved, although insufficiently to return to normal life making OLT an inevitable outcome. Individual variation in response to UDCA can be related to pre-existing liver damage or to different mutations (Stop codon, missense mutation) affecting the bile acid or the phosphatidylcholine transporter function at various degrees (12, 15*)*

Partial biliary drainage was unsuccessful in 3 out of five patients, and partially successful in 2. This surgery may only be indicated in patients with effective bile acid secretion, but not if biliary bile acid levels are extremely low and not if cirrhosis is already established (16, 21, 22).

Liver transplantation remained the final option for the majority of our patients, allowing these children to return to normal life, with more than 90% survival rate 5 years after OLT. This excellent survival rate may also be linked to a satisfactory general state with no history of previous surgery. The timing of OLT remains difficult to establish since in many patients indication for OLT is more often related to the poor quality of life than to end stage liver disease or liver failure.

Finally, hepatocyte transplantation has been shown to correct liver disease in the mouse model of PFIC3 disease (23). Cell therapy is a safe and promising technique in the treatment of liver based inborn errors of metabolism and may become an indication for the PFIC patients (24).

Conclusion

There are many clinical, biochemical and histological similarities between the different subtypes of PFIC. The only significant clinical difference is the intensity of pruritus. However serum GGT and liver biopsy helps in classifying PFIC III from PFIC I and II patients. Because high levels of biliary bile acids in low-GGT patients seems to indicate a better prognosis, we suggest that quantitative bile acids analysis in serum urine and bile should be performed in all PFIC patients. Response to UDCA varies from patient to patient and is not always linked to subtypes of PFIC. However it should be started as soon as PFIC is suspected. In this cohort external biliary drainage was not beneficial. We recommend to propose transplantation whenever medical treatment fails to restore normal social life, growth and well being of the child.

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