Cholestase Intra-hépatique Récurrente Bénigne

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Cas Clinique

- **Homme de 29 ans, d'origine Marocaine, motif de consultation: prurit sévère et ictère (10/2011)**
- **Antécédents:**
  - CIV opéré à l'âge de 3 mois
  - Vacciné contre VHB
  - Épisode inexpliqué de prurit en 2010 (15 j)
  - Diarrhée fréquente depuis 2 ans
  - Ni alcool, ni tabac, ni médicament, ni drogue
- **Histoire récente (09/2011):**
  - Gastro-entérite aiguë début septembre
  - Puis apparition d'un prurit, asthénie, anorexie, puis ictère et selles décolorées, perte de 2 Kg

Cas Clinique (suite)

- **Examen clinique:**
  - Poids 67 kg, taille 1,65 m, apyrexie
  - Ictère cutanéo-muqueux, lésions de grattage
  - Ni organomégalie, ni adénopahtie
- **Examens biologiques standards:**
  - Bilirubine totale: 330 µM, conjuguée: 320 µM
  - PAL: 155 UI/l (N<129); GGT: 40 UI/l (N<61)
  - ALAT: 210 UI/l (n<40); ASAT: 111 UI/l (N<40)
  - NFS-plaquettes: normale
  - Albumine: 37 g/l; Gammaglobulines: 11 g/l
  - TP: 33% (Facteur V: 100%)

Cas Clinique (suite)

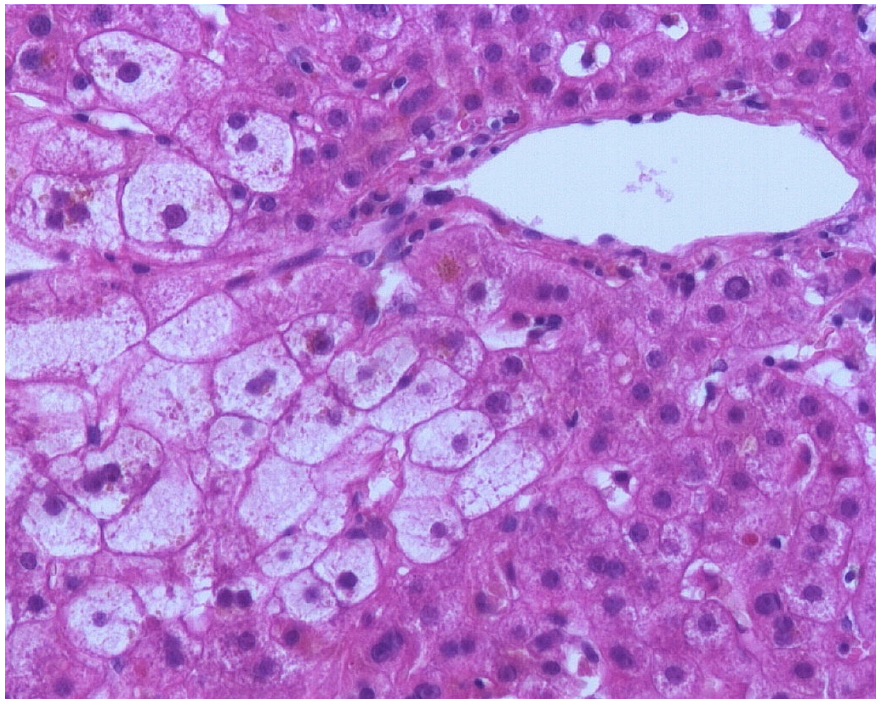
- **Examens d'imagerie:**
  - Echographie hépatique: normale
  - Cholangio-IRM: normale
- **Examens étiologiques:**
  - IgM anti-VHA: négatif
  - Ag HBs et IgM anti-VHB: négatifs
  - Sérologie VHC: négatif
  - IgM anti-VHE et PCR VHE: négatifs
  - PCR CMV et PCR EBV: négatifs
  - Anticorps anti-tissus: négatifs
  - Bilan martial et cuivre: normal

Cas Clinique (suite)

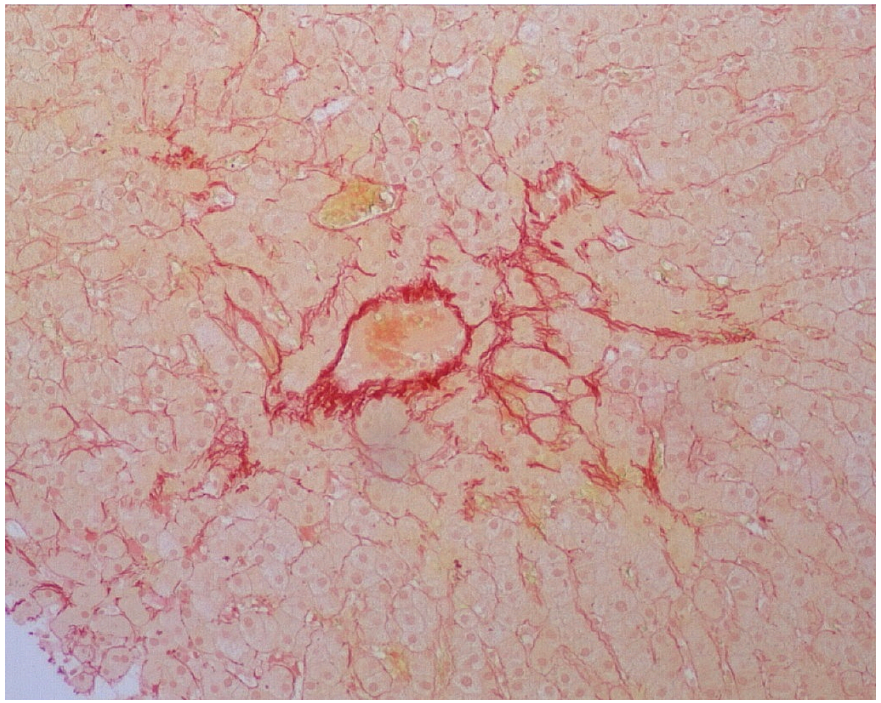
- **Dosages sériques des acides biliaires:**
  - Acides biliaires totaux: 227 µM
  - Acide cholique **(CA)**: 176 µM
  - Acide chénodéoxycholique **(CDCA)**: 50 µM
  - Acide déoxycholique **(DCA)**: 0 µM
  - Acide lithocholique **(LCA)**: 0,1 µM
  - Acide ursodéoxycholique **(UDCA)**: 0,1 µM
- **Examens endoscopiques (diarrhée):**
  - Iléo-coloscopie (+ biopsies): normale
  - Gastroscopie (+ biopsies): normale

Cas Clinique (suite)

- **Examen histologique du foie (biopsie):**



Cholestase centrolobulaire marquée



Discrète fibrose centrolobulaire

Cas Clinique (suite)

- **En résumé:**
  - Cholestase ictérique intra-hépatique quasi-pure
  - Prurit sévère
  - GGT normale
  - Sujet jeune
  - Pas de médicament
  - Possible épisode a minima il y a 1 an
  - Après ré-interrogatoire: notion de consanguinité familiale
- **Hypothèse principale: BRIC**

Cas Clinique (suite)

- **Traitement du prurit:**
  - Cholestyramine 12 g/j: **échec**
  - Rifampicine 600 mg/j: **échec**
  - Naltrexone 50 mg/j: **échec**
  - Echanges plasmatiques 1 à 2/sem: **effet partiel**
- **Evolution:**
  - Nov 2011 **(M2)**: Bili 279 µM, ALT 2N, prurit +++
  - Dec 2011 **(M3)**: Bili 160 µM, ALT 4N, prurit ++
  - Jan 2012 **(M4)**: Bili 15 µM, ALT 2N, prurit +
  - Fev 2012 **(M5)**: Bili 5 µM, ALT N, prurit -

Cas Clinique (suite)

- **Analyse génétique:**
  - ***ATP8B1*** **(FIC1):**
    - ✓ **Mutation homozygote de l'exon 16**
    - ✓ Nomenclature protéique: **His630Pro**
    - ✓ Conséquence: mutation faux-sens (prédite comme délétère)
  - ***ABCB11*** **(BSEP):**
    - ✓ **Variant homozygote de l'exon 13**
    - ✓ Nomenclature protéique: **Val444Ala**
    - ✓ Conséquence: variant faux-sens (associé au risque d'ICP et de cholestase hormonale)

Cas Clinique (fin)

- **Diagnostic définitif: BRIC1**
- **Evolution:**
  - Seconde poussée sévère de 09/2012 à 01/2013
  - Est depuis sous AUDC 200 mg x 2/j
  - Va bien
  - Discrète cytolyse par moment

Cholestase Récurrente Bénigne (1959-1960)

due to arteriosclerosis. The diagnosis of cases treated conservatively must rest upon clinical grounds or post-mortem evidence. In "recovered" cases the lesion is a matter of clinical impression, as in the many reports of the conservative treatment of so-called subarachnoid hæmorrhage. It is equally difficult to compare our cases with other surgically treated cases for our series has been consecutive and entirely unselected by us, no patient being deemed too ill for investigation and treatment although many were moribund on admission.

Considering the gravity of the disease, a survival of only 65 out of 244 is not perhaps as disappointing as it may appear; but it should certainly stimulate neurosurgeons to a deeper interest in this challenging problem.

In this paper we have reviewed what has been achieved in the past, largely with the idea of planning our investigations and design for the future. A number of facts emerge, of which the most important is probably the lack of a series of comparable cases, treated by conservative means alone, against which to assess the advantages or disadvantages of surgical methods of treatment. The accuracy of 70% offered by angiography in the diagnosis of these lesions is too imprecise, and it is obviously desirable that some other diagnostic measure, short of surgical intervention, should be devised. Because the mere introduction of a brain cannula into a hæmatoma cavity may well alter the prognosis, this means could hardly be used to establish the diagnosis of hæmorrhage in a series of cases designed to be treated medically. A single method of surgical treatment should be chosen which can be used in a random set of patients and assessed against a similar series treated conservatively.

Further, the metabolic effects of these lesions require additional study: we know little of the general disturbances occasioned by the ictus or of the local alterations in the C.S.F., although both these factors may militate against a successful outcome. Whilst not losing sight of the desirability of removing a space-occupying hæmatoma, we must not ignore these secondary metabolic disturbances which may rob us of surgical success. Much work has been done on similar problems in cases of head injury (Tower and McEachern 1949a and b, Higgins 1954), in epileptics (Tower and McEachern 1949a and b), and in patients submitted to cranial surgery (*Lancet* 1958), but little has been done in the field of intracerebral hæmorrhage. Cerebral anoxia produced by congestion, unconsciousness, and the accumulation of secretions in the nasopharynx and trachea, must play a part in the deterioration of these patients, and it may well be made worse by angiography. We feel that early tracheostomy has its place in treatment, possibly even before radiological investigations; for it has certainly proved its worth as a postoperative measure in cerebral surgery, and in the treatment of severe head injuries.

In the coming years we hope to assess surgical methods of treatment as against active conservative measures, due consideration being given to the history, clinical state, and modes of investigation in relation to age, sex, hypertension, state of consciousness, and time since the ictus.

Summary

A consecutive series of 244 cases of proven primary intracerebral hæmorrhage is reported.

The absence of blood in the lumbar or ventricular fluid in 20% of these cases is noted in relation to the difficulties of of purely clinical diagnosis.

The factors influencing mortality are: (1) the site but not the size of the lesion (capsular hæmorrhages carrying the worst prognosis), (2) hypertension, which is unfavourable, and (3) the state of consciousness at the time of operation, the death-rate rising as the level of consciousness falls.

The urgent use of ancillary methods of diagnosis (angiography and sometimes exploratory burr-holes) is emphasised.

The various methods of surgical treatment employed are related to the state of consciousness of the patients.

The immediate operative mortality was 51%. Subsequent deaths, from various causes, raised the total mortality to 74%.

Of the 63 survivors 25 are well, and only 6 are totally disabled.

Various lines of research are contemplated. There is need for a controlled series of cases treated by conservative measures.

We should like to thank the Wolfson Foundation for the research grant made to A. R., which has helped to make this work possible.

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BENIGN RECURRENT INTRAHEPATIC "OBSTRUCTIVE" JAUNDICE

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MANY disorders with differing clinical and metabolic features are classified as "constitutional hyperbilirubinæmia". Gilbert and Lireboullet (1901) drew attention to the occurrence of benign non-hæmolytic jaundice without bile in the urine, but it is now considered that several diseases may give similar findings (Foulk et al. 1959), including the group of patients specified by Crigler and Najjar (1952). In addition, a constitutional hyperbilirubinæmia with obstructive features has been described (Dubin and Johnson 1954, Sprinz and Nelson 1954). It is characterised by the presence of bile in the urine and pigment in the hepatic cells, and many further examples have since been recognised (Dubin 1958).

We report here two cases of benign recurrent jaundice with obstructive features, which differ in several essential respects from those summarised by Dubin (1958), and which cannot be classified within the existing nomenclature of liver disease.

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Summerskill & Walshe. Lancet 1959

INTERMITTENT POSSIBLY FAMILIAL INTRAHEPATIC CHOLESTATIC JAUNDICE

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IN recent years several new syndromes of jaundice have been recognised, some of which are thought to be due to inborn errors of metabolism (Meulengracht 1947, Crigler-Najjar 1952, Dubin 1958). Furthermore a number of cases of chronic cholestatic jaundice, probably belonging to the same group of diseases, have been described (Rotor et al. 1948, Stransky 1950, Schiff et al. 1959, Davis and Young 1959, Haverback and Wirtschafter 1959, Summerskill and Walshe 1959), but the cases have been too few for syndromes to be clearly defined.

At an interval of one year two boys, each 15 years of age, were examined at Rigshospitalet, Copenhagen, on account of intermittent jaundice since early childhood. They belonged to the same small community (9000 inhabitants) in the Faroe Islands, and claimed to be related to each other, although the nature of their relationship could not be established. There were no other known cases of jaundice in that particular island when jaundice appeared in the boys; there were no familial cases apart from these two; and neither patient had had neonatal jaundice.

Case-records

Case 1 had had attacks of jaundice, lasting two to three months, at the age of 2 and 4 years. He was then well until the age of 12, when jaundice recurred and laparotomy was performed. No gross abnormality of liver or bileducts was found (no biopsy ' or cholangiography), but cholecystogastrostomy was undertaken. Two months later jaundice disappeared, but three years later it recurred after an attack of Asian influenza. On admission to Rigshospitalet the patient felt tired, had poor appetite, and was losing weight. Skin and sclerae were much jaundiced; there was no hepatosplenomegaly, spider nævi, ascites, or œdema. The laboratory findings are shown in the accompanying table.

LABORATORY DATA

Test	Case 1	Case 2
Serum-bilirubin (mg. per 100 ml.):	34·8	14·9
% direct reaction, 10 min.	Not done	85
Serum-alkaline-phosphatase (K.A. units)	94	49
*Thymol turbidity**	0·04	0·02
S.G.O.T.	6·0	3·4
S.G.P.T.	1·0	11·0
Eosinophils (per µl.)	40	500
Serum-potassium (mEq. per litre)	2·8	4·0
Serum-cholesterol:		
Total (mg. per 100 ml.)	234	386
Free (%)	62	29
Fæcal fat (g. per 24 hr.)	48	14
Serum-albumin (g. per 100 ml.)	3·1	3·1
Serum-α-globulin (g. per 100 ml.)	1·5	1·0
Serum-β-globulin (g. per 100 ml.)	1·5	1·5
Serum-γ-globulin (g. per 100 ml.)	0·7	1·0
Urine-bilirubin	+ + +	Not done
Urine-urobilinogen	Neg.	Not done
Oral and intravenous cholecystography	Not displayed	Not displayed
Gbadim-Weinberg and Casoni test †	Not done	Neg.
Toxoplasma complement-fixation test	Not done	Neg.

* Extinction units: normally less than 0·14. † Echinococcus test.
S.G.O.T.=serum-glutamic-oxalacetic-transaminase. Normally less than 1·7 units.
S.G.P.T.=serum-glutamic-pyruvic-transaminase. Normally less than 1·6 units.

Case 2 had been jaundiced with remarkable regularity for two to three months at a time, with free intervals of the same duration, from the age of 1 to the age of 7 years. At laparotomy when he was 6 years of age the liver and biliary tracts were macroscopically normal (no biopsy or cholangiography).

Between the age of 7 and 15 he had no jaundice and developed normally. Then he had a further attack, and after two months was admitted to Rigshospitalet. The findings were essentially the same as in the first patient. Furthermore this patient was found to be allergic to eggs and milk, and the peripheral blood contained slightly increased numbers of eosinophils. Although the patient recalled no coincidence of his allergic manifestations (vomiting and diarrhœa) and the periods of jaundice, the cause of the jaundice was thought to be possibly allergic. Therefore prednisone 40 mg. daily was given for three weeks; but the serum-bilirubin level was unchanged, and he returned to the Faroe Islands unimproved. Four months later, according to his doctor, his condition had deteriorated and he was still losing weight; but after a further two months his condition was improving, jaundice and itching had disappeared, and he was able to continue school after an interruption of more than six months.

Discussion

From the clinical, biochemical, and histological findings it must be concluded that in these two cases the jaundice was due to intermittent intrahepatic cholestasis. The most common causes of intrahepatic cholestasis—viral hepatitis and certain drugs—can be ruled out in the present cases. The most likely mechanism is some defect in the excretion of bilirubin by the liver cells, similar to that suggested by Dubin (1959) in chronic idiopathic jaundice (Dubin-Johnson syndrome), or an allergic "cholangiolitis" (which is supposed to be the cause of chlorpromazine jaundice); but the nature and the site of the lesion in intrahepatic cholestatic jaundice remains obscure (Popper and Szanto 1956).

The cases described by Rotor et al. (1948), Stransky (1950), Schiff et al. (1959), Davis and Young (1959), and Haverback and Wirtschafter (1959) probably belong to one group, differing from the present cases in being more constantly, though not so deeply jaundiced, and in having an histologically normal liver, normal liver-function tests (including serum-alkaline-phosphatase), and normal appearance of the gallbladder at oral cholecystography; but the difference may be merely quantitative. The two cases described by Summerskill and Walshe (1959) correspond closely to the present ones, except that in these the jaundice first appeared much earlier, the patients were probably related, indicating a hereditary factor, and the patients' general condition was much affected during the

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Tygstrup. Lancet 1960

Cholestase Récurrente Bénigne

A chemical or physicochemical disorder affecting the transport of individual components of the bile across the liver-cell membrane or in the bile canaliculi and capillaries must therefore be considered—probably one affecting those constituents, such as bile pigments and salts, which are highly concentrated by an active mechanism.

On two occasions a T-tube was left in the common bileduct after laparotomy, for periods of six and seven months, and the jaundice cleared. The significance of this is uncertain, especially as drainage of the common bileduct hastens recovery from intrahepatic jaundice due to hepatitis (McSwain et al. 1958) as well as from extrahepatic jaundice.

Summerskill & Walshe. Lancet 1959

BRIC: Critères Cliniques

1) Au moins 2 épisodes d'ictère cholestatique avec prurit (mais l'ictère ou le prurit peut manquer)
2) GGT normale ou peu élevée
3) Cholangiographie normale
4) Cholestase centrolobulaire isolée (PBH requise)
5) Absence de médicament / toxique
6) Intervalles libres de plusieurs mois ou années

Tygstrup et al. Acta Med Scand 1969
Luketic et al. Clin Liver dis 2004

BRIC: Variabilité Clinique

- **Début à l'âge adulte: 30% à 50%**
- **Cas sporadiques: 50% à 90%**
- **Durée des crises: 2 semaines à 24 mois (3 mois en moyenne)**
- **Durée des intervalles libres: 1 mois à 33 ans**
- **Nombre total de crises: 1 à 30 (1 crise tous les 2 à 3 ans en moyenne)**
- **Evolution vers une forme sévère permanente: 5%**

Brenard et al. J Clin Gastroenterol 1989
Luketic et al. Clin Liver dis 2004
Van Ooteghem et al. J Hepatol2002

BRIC: Variabilité Clinique (suite)

Patient	Gender	Age at diagnosis (years)	Country	Number of attacks: total/before 20 years
1	M	15	France	3/3
2	M	46	France	12/0
3	F	20	France	3/3
4	F	25	Belgium	2/1
5	F	62	Italy	2/0
6	F	53	Belgium	4/0
7	F	20	Caribbean Islands	1/1
8	F	35	France	6/1
9	M	41	France	2/0
10	M	45	Zaire	2/0
11	F	50	France	8/1
12	F	46	France	7/1
13	F	30	France	3/0
14	M	40	Egypt	3/0
15	F	37	France	8/1
16	M	50	Morocco	1/0
17	M	25	Italy	10/0
18	F	23	France	3/2
19	M	19	France	3/2
20	F	32	France	5/0
21	M	38	France	5/1
22	M	21	Belgium	5/4
23	F	48	Germany	2/0
24	M	52	Italy	2/0
25	M	51	Algeria	7/2
26	F	53	Belgium	3/0

Patient	Serum bilirubin (μmol/L)	AP (N)	GGT (N)	GOT (N)	GPT (N)
1	161	7	—	4	8.6
2	144	6	—	2.6	4.9
3	65	1	—	6.3	4
4	357	3.8–5	1	4.4–5.3	3.8
5	374	2.5–3.3	10	2–22	1.5–47
6	370	6	2	4	—
7	120–250	3–40	3–75	2–7	2–9
8	150	1	1	1.8	3.4
9	450–750	4	3	2–50	2–65
10	400	1.2	3	1	1.5
11	105–300	3–10	2	1–22	1.2–30
12	—	—	—	—	—
13	93	1	—	—	4
14	200–550	10	—	3.5–9	5–18
15	32	—	—	—	3
16	350	5	—	—	3.3
17	290–850	3	1	2.1	1
18	16[a]	4.1[a]	2.8[a]	2.4[a]	3[a]
19	91	2	—	—	—
20	28	2.2	3.5	3.1	7.7
21	305–463	3.9–5	1–1.5	1.1–5.4	1–7.5
22	51–240	1.5–6.8	4–5.3	1.5–4.6	4.2–13
23	219	3.5	1	2.3	3.4
24	330	2.8	3.6	2.7	2
25	80	2.9	—	4.3	6.9
26	100	1.5	1.2	4.1	7.5

Brenard et al. J Clin Gastroenterol 1989

BRIC: Histopathologie

Patient no.	Centrilobular cholestasis	Infiltration of portal spaces with mononuclear cells	Other findings
1	+	0	Mild portal fibrosis
2[a]	0	0	0
3	+	0	0
4	++	0	0
5	++	0	0
6	++	0	0
7	++	+ (and eosinophils)	Ductular proliferation
8	++	0	Mild intralobular infiltration with mononuclear cells
9	++	+	Mild intralobular infiltration with mononuclear cells
10	++	0	0
11	++	+	0
12	–	–	—
13	+	0	Mild sinusoidal dilatation
14	–	–	—
15	++	0	0
16	++	0	0
17	–	–	—
18[b]	0	+	0
19	+	0	0
20	++	0	0
21	++	+	0
22	++	+	0
23	++	0	0
24	++	0	0
25	–	–	—
26	+	+	0

–, Biopsy not performed; 0, absent; +, mild; ++, intense.
[a] Biopsy performed between 2 attacks.
[b] Biopsy performed 5 months after the third attack of cholestasis.

Brenard et al. J Clin Gastroenterol 1989

BRIC: Rares Formes de Passage vers PFIC

Benign recurrent intrahepatic cholestasis progressing to progressive familial intrahepatic cholestasis: low GGT cholestasis is a clinical continuum

Nancy A.M. van Ooteghem[1,*], Leo W.J. Klomp[2,3],
Gerard P. van Berge-Henegouwen[1], Roderick H.J. Houwen[2]

Patients	First cholestatic attack at	Permanent cholestasis	First liver biopsy in early stage (age)	Liver biopsy in late stage (age)
1	15 months	Third decade	Characteristic for BRIC (16 years)	Porto-portal fibrotic septa (22 years)
2	6 months	Third decade	Normal liver structure (1/2 year)	Intra-acinar cholestasis, porto-portal fibrosis (27 years)
3	14 months	Fourth decade	Normal liver structure, no fibrosis (11 years)	Preserved liver structure with steatosis and the beginning of formation of porto-portal septa (35 years)
4	6 months	Second decade	Normal liver structure, no fibrosis (1/2 year)	Canalicular cholestasis, severe fibrosis (10 years)

Van Ooteghem et al. J Hepatol 2002

A Case of Severe Benign Intrahepatic Cholestasis Treated With Liver Transplantation

Esteban Mezey, Clinton Burns, James F. Burdick, and Hayden G. Braine
Departments of Medicine and Surgery, The Johns Hopkins University School of Medicine, Baltimore, Maryland

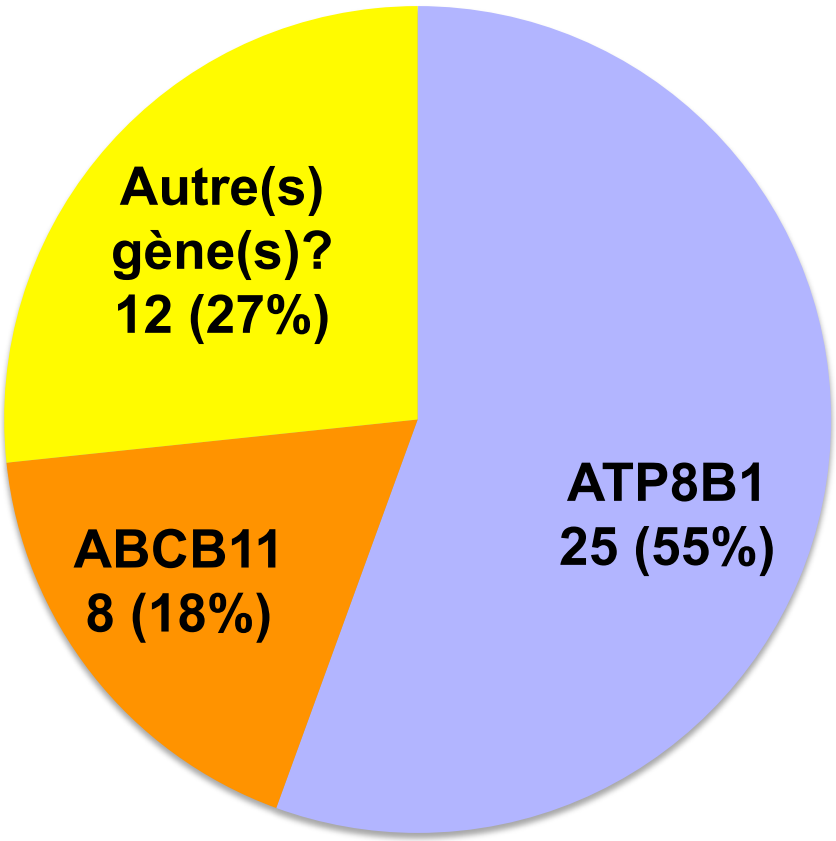
Mezey et al. Am J Gastroenterol 2002

BRIC: Origine et Hétérogénéité Génétique

BRIC	**Type 1**	**Type 2**	
PFIC	**Type 1**	**Type 2**	**Type 3**
Localisation	18q21-22	2q24-31	7q21
Gène (protéine)	**ATP8B1 (FIC1)**	**ABCB11 (BSEP)**	ABCB4 (MDR3)
Transport	Phosphatidylsérine	Acides biliaires	Phosphatidylcholine
GGT	Normale	Normale	Elevée
ICP	Oui	Oui	Oui ++
Lithiase biliaire	Non	Oui	Oui ++ (LPAC)
DILI	Possible	Oui	Possible
Autres	Surdité Pancréatite Malabsorption Pneumopathie	CHC (PFIC2)	CHC CCA

BRIC: Hétérogénéité Génétique (suite)

45 familles testées pour ATP8B1 et ABCB11

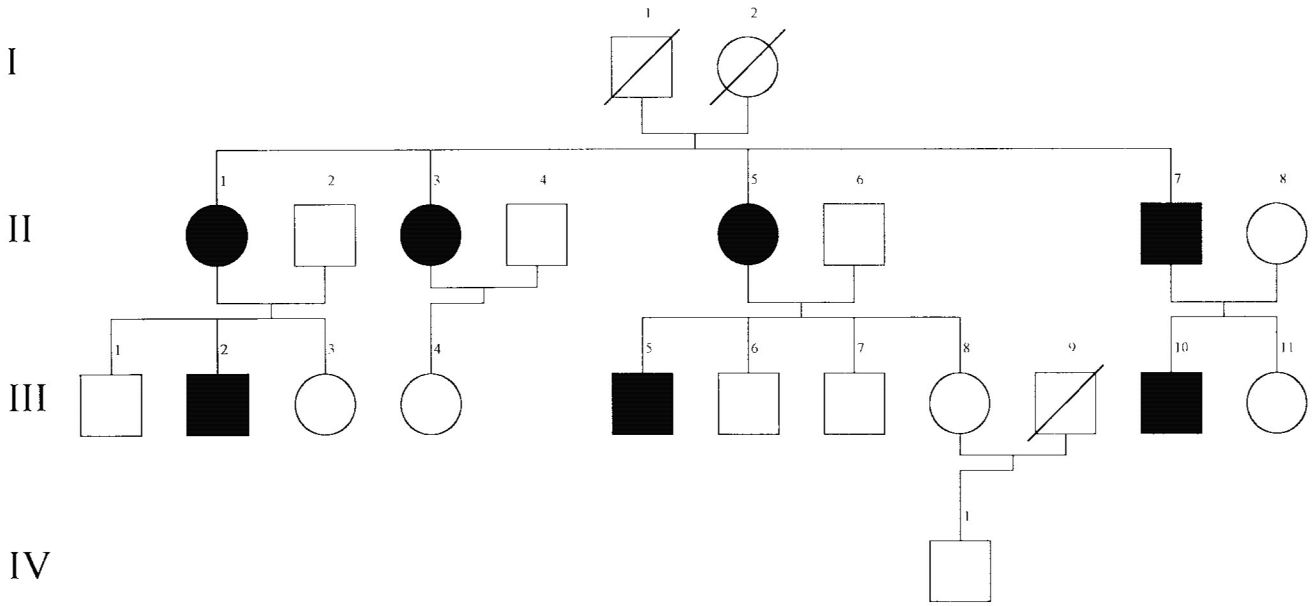


Klomp et al. Hepatology 2004
Saskia et al. Gastroenterology 2004

BRIC: Hétérogénéité Génétique (suite)

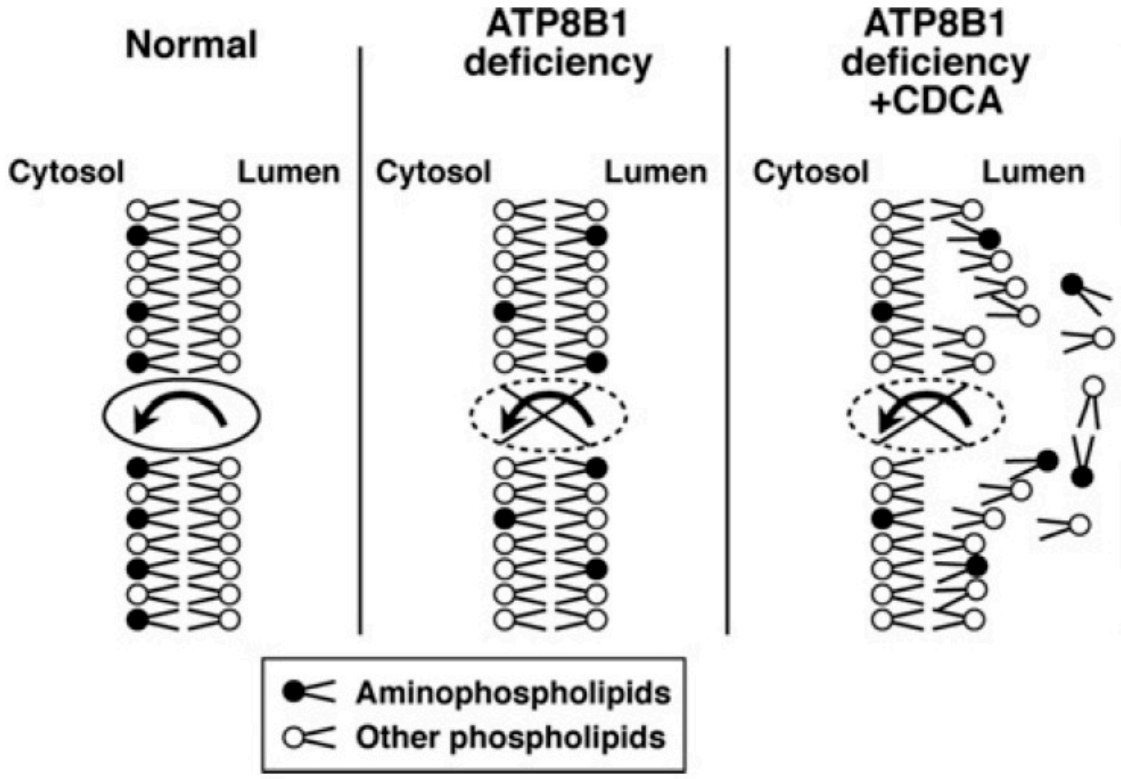
Brief Clinical Report

Autosomal Dominant Benign Recurrent Intrahepatic Cholestasis (BRIC) Unlinked to 18q21 and 2q24



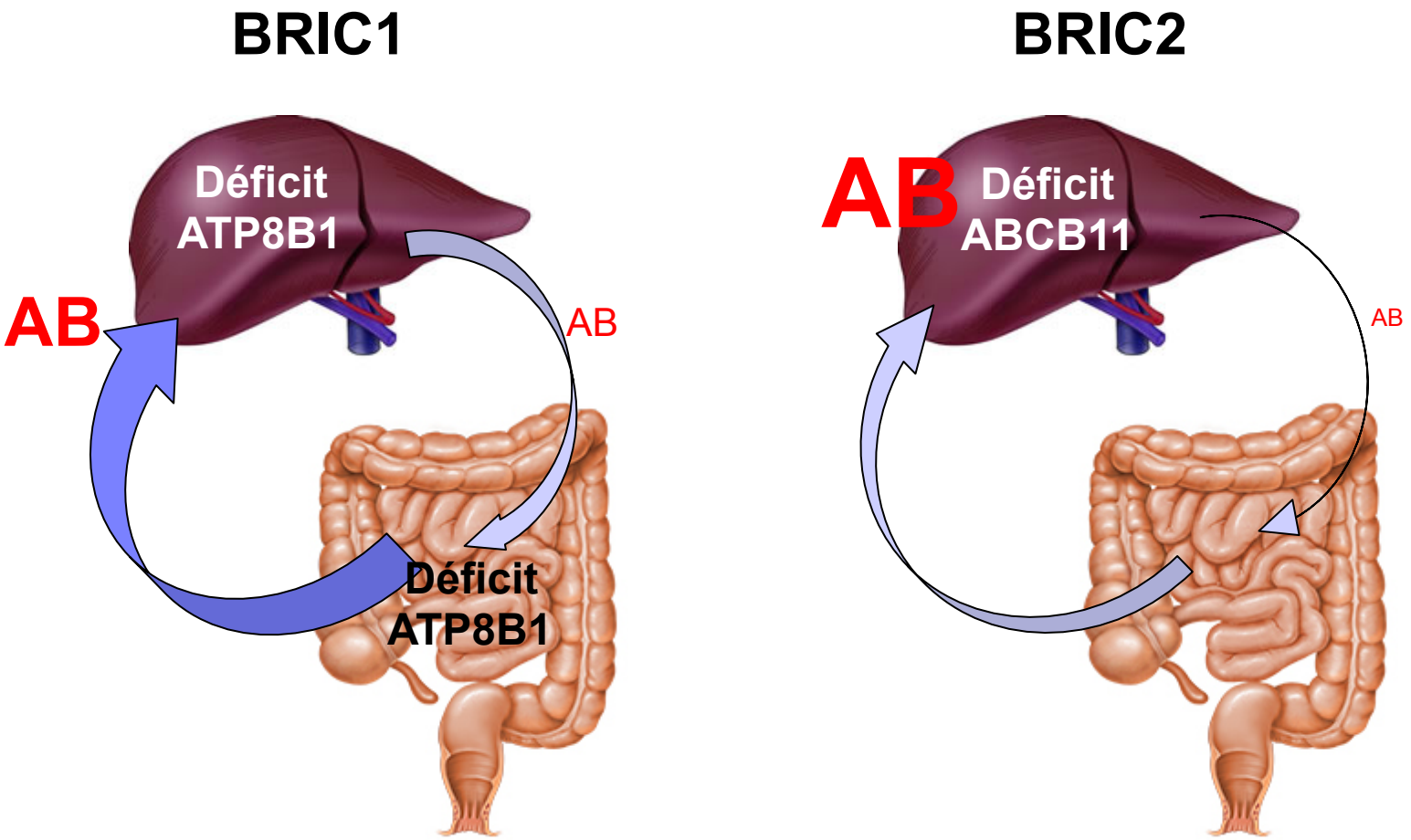
Floréani et al. Am J Med Genet 2000

BRIC: Fonction de ATP8B1?



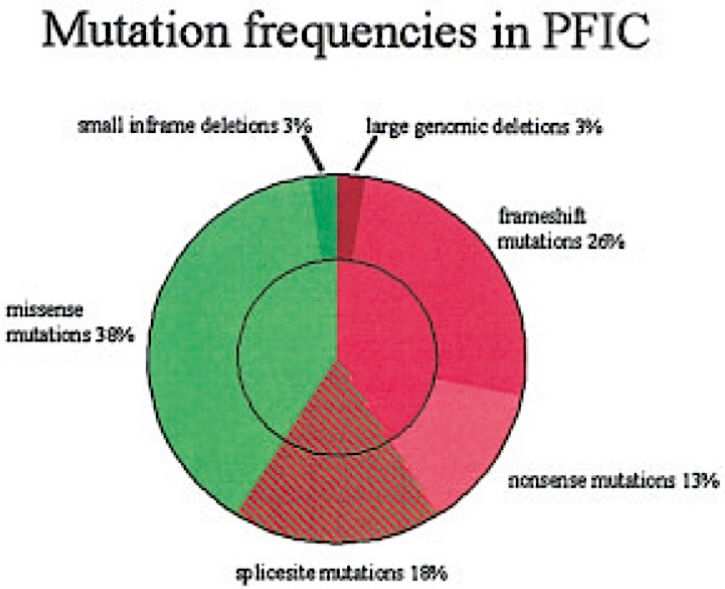
Cai et al. Gastroenterology 2009

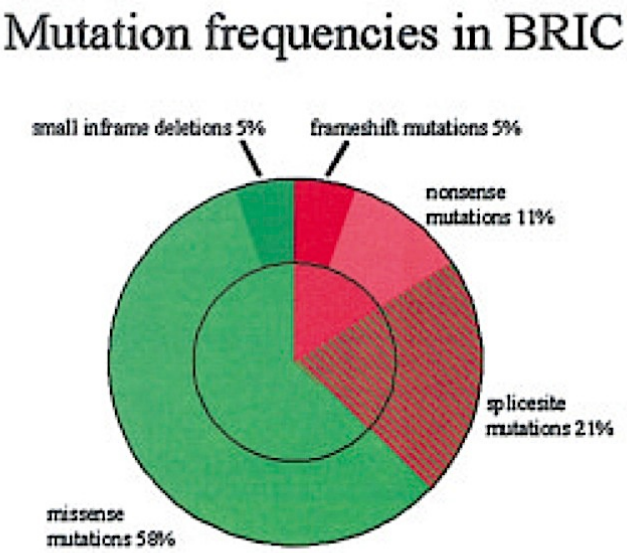
BRIC: Physiopathologie



Pawlikowska et al. Hum Mol Genet 2004

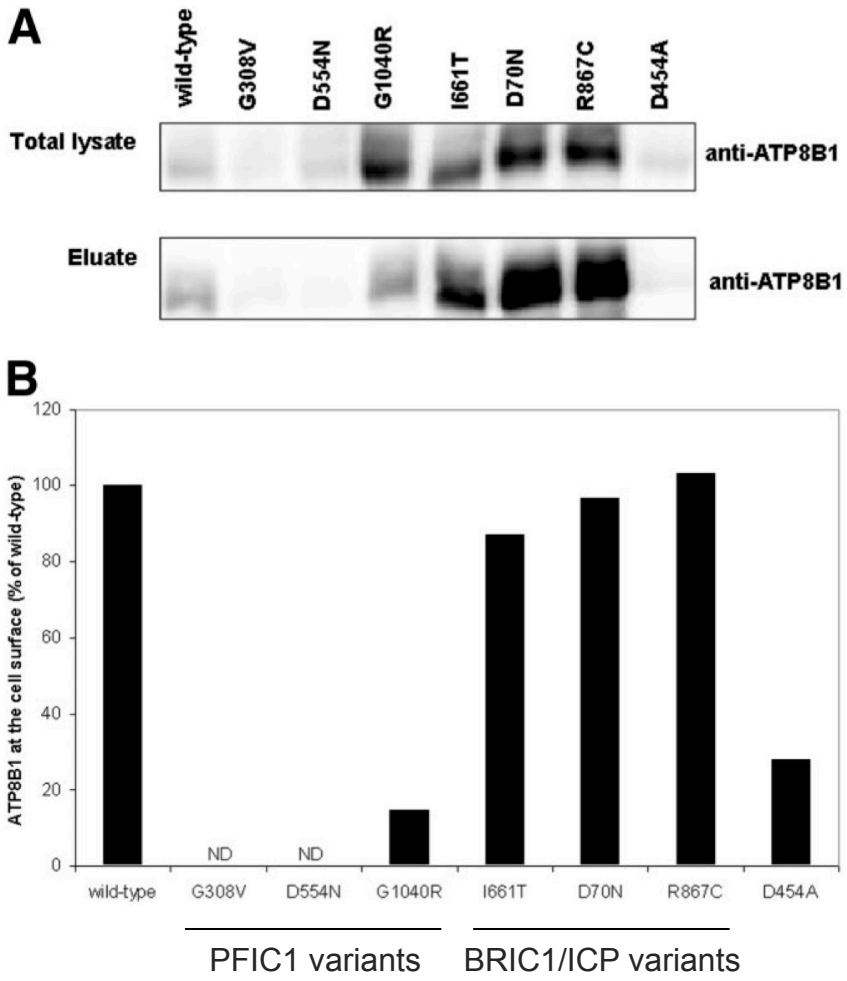
ATP8B1: Corrélation Génotype-Phénotype





Klomp et al. Hepatology 2004

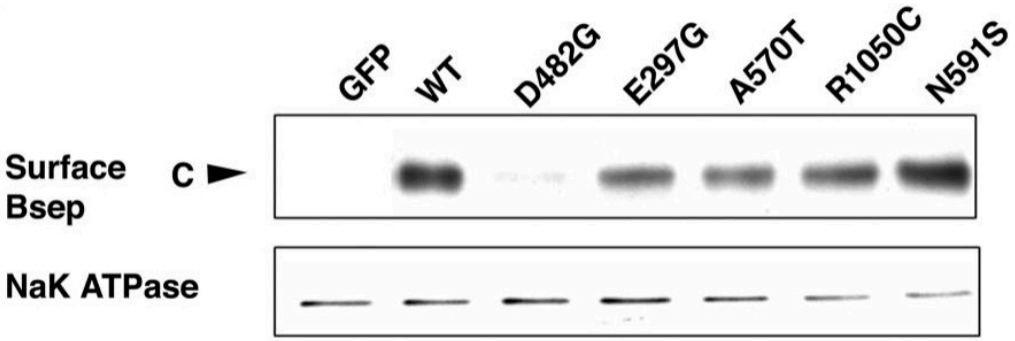
ATP8B1: Corrélation Génotype-Phénotype

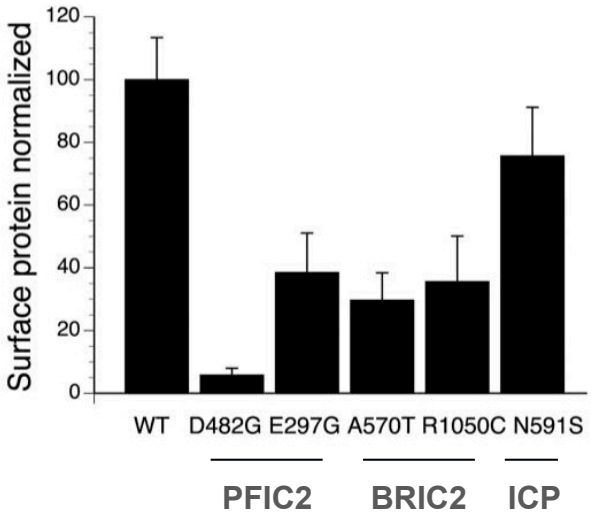


Folmer et al. Hepatology 2009

ABCB11: Corrélation Génotype-Phénotype

ABCB11 point mutations

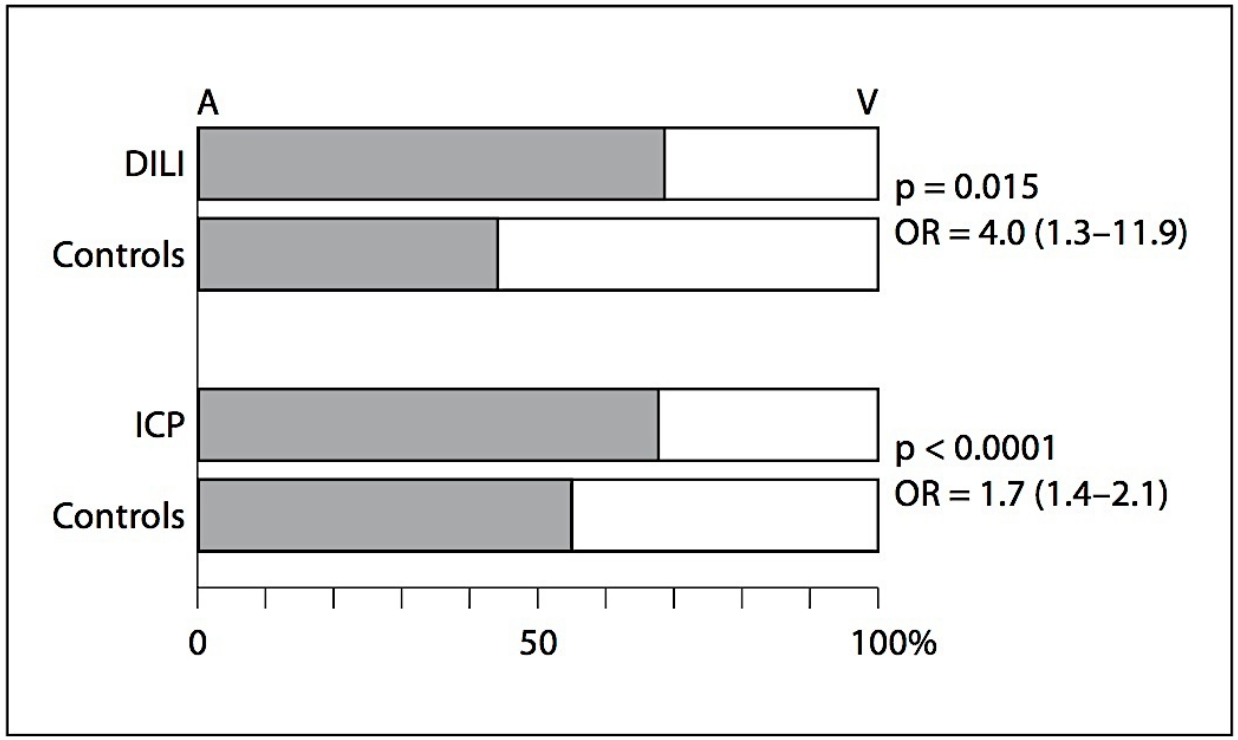




Lam et al. Am J Physiol Cell Physiol 2007

ABCB11: Rôle du Variant Fréquent V444A

ABCB11 p.V444A allele distribution



Müllenbach et al. Dig Dis 2011

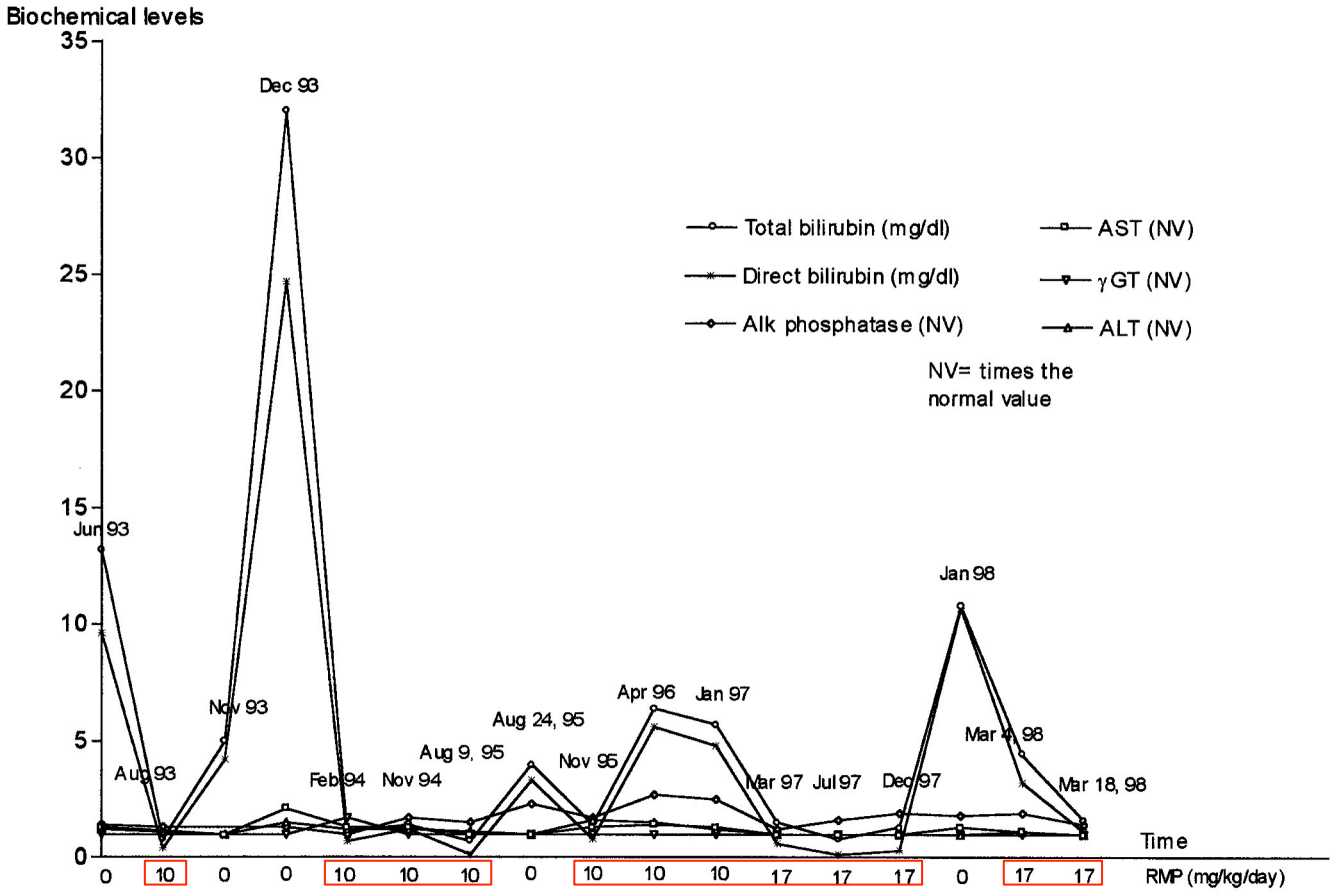
BRIC: Options Thérapeutiques

Aucun traitement curatif ou préventif d'efficacité démontrée

Traitements non-invasifs	Traitements invasifs
Antihistaminiques	**Echanges plasmatiques**
Cholestyramine	**Dialyse Albumine (MARS)**
Corticoïdes	**Drainage naso-biliaire**
Phénobarbital	**Dérivation biliaire partielle**
AUDC	**Exclusion iléale (bypass)**
Rifampicine	Transplantation hépatique
Naltrexone	
Sertraline	
Photothérapie UVB	

En gras: traitements susceptibles de raccourcir les crises

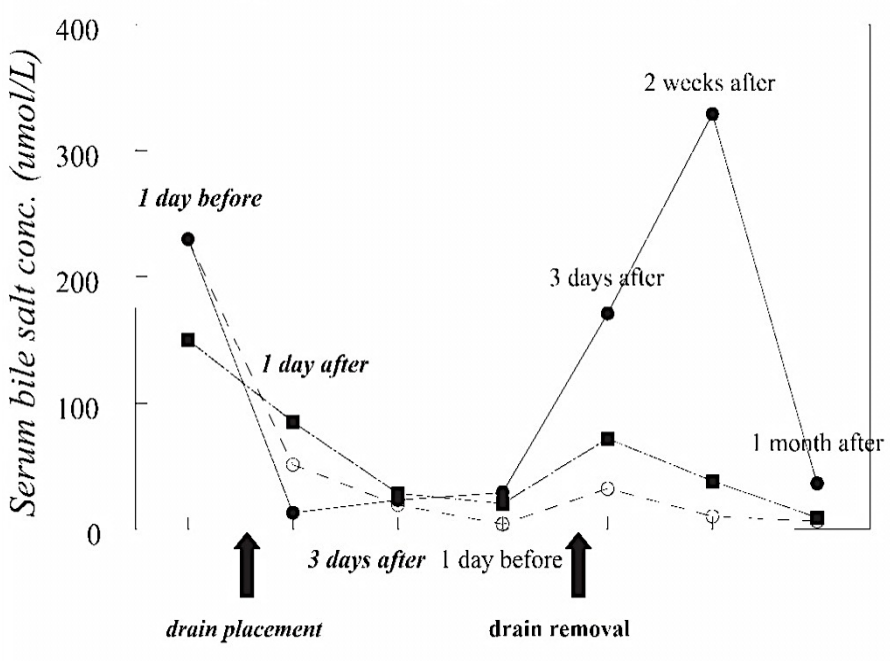
BRIC: Rifampicine (5-15 mg/kg/j)

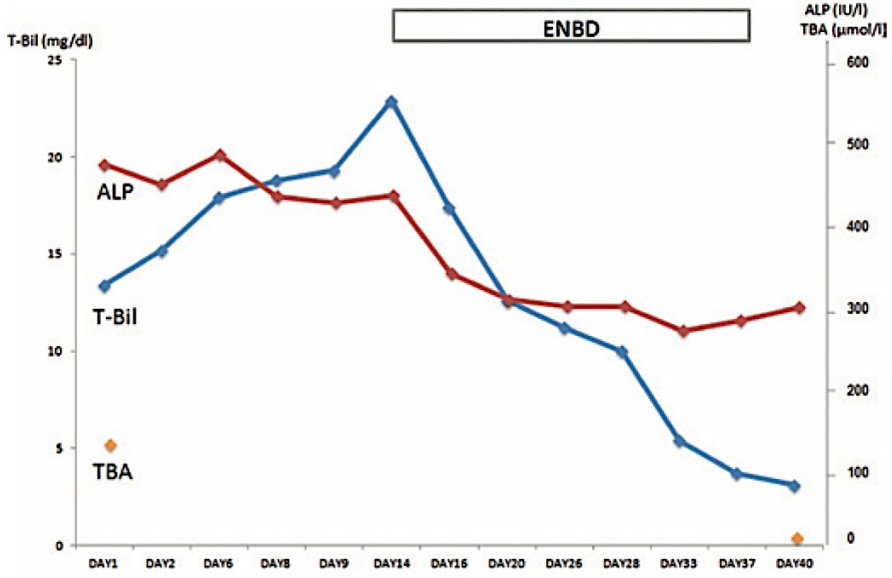


Cançado et al. Am J Gastroenterol 1998

BRIC: Drainage Naso-biliaire (3-5 semaines)

Le drainage naso-biliaire est probablement l'option la plus logique et la plus efficace dans cette situation pathologique



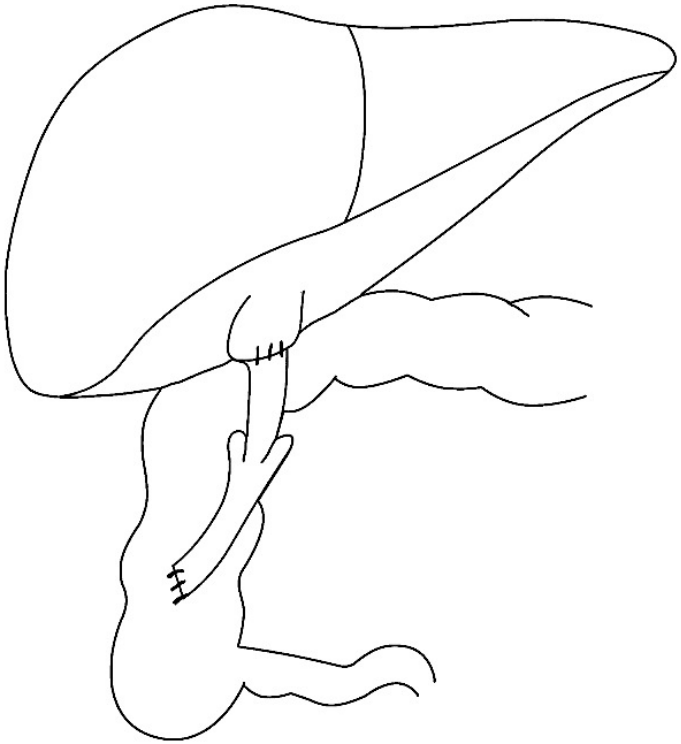


Stapelbroek et al. Hepatology 2006

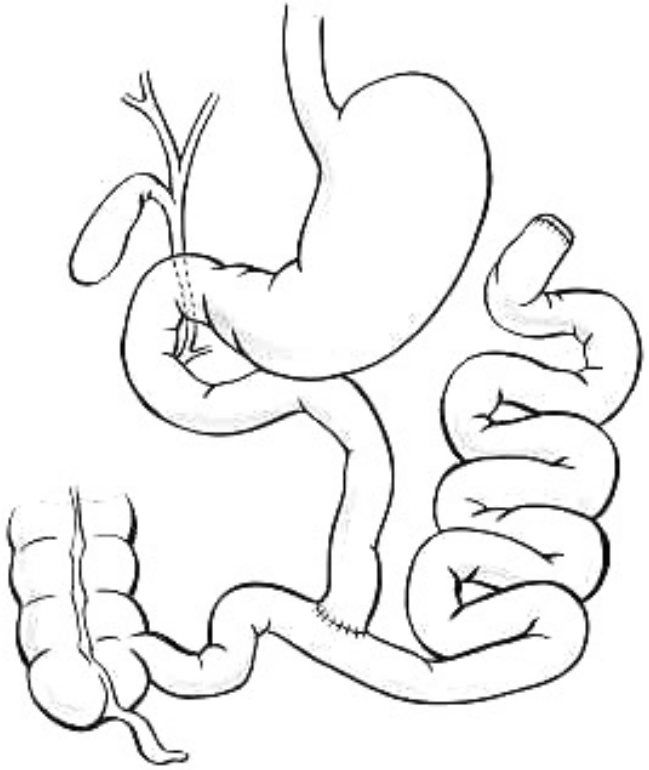
Wakui et al. Exp Ther Med 2013

BRIC: Dérivation Biliaire Partielle & Bypass

En cas de formes sévères avec rechutes fréquentes ou permanentes



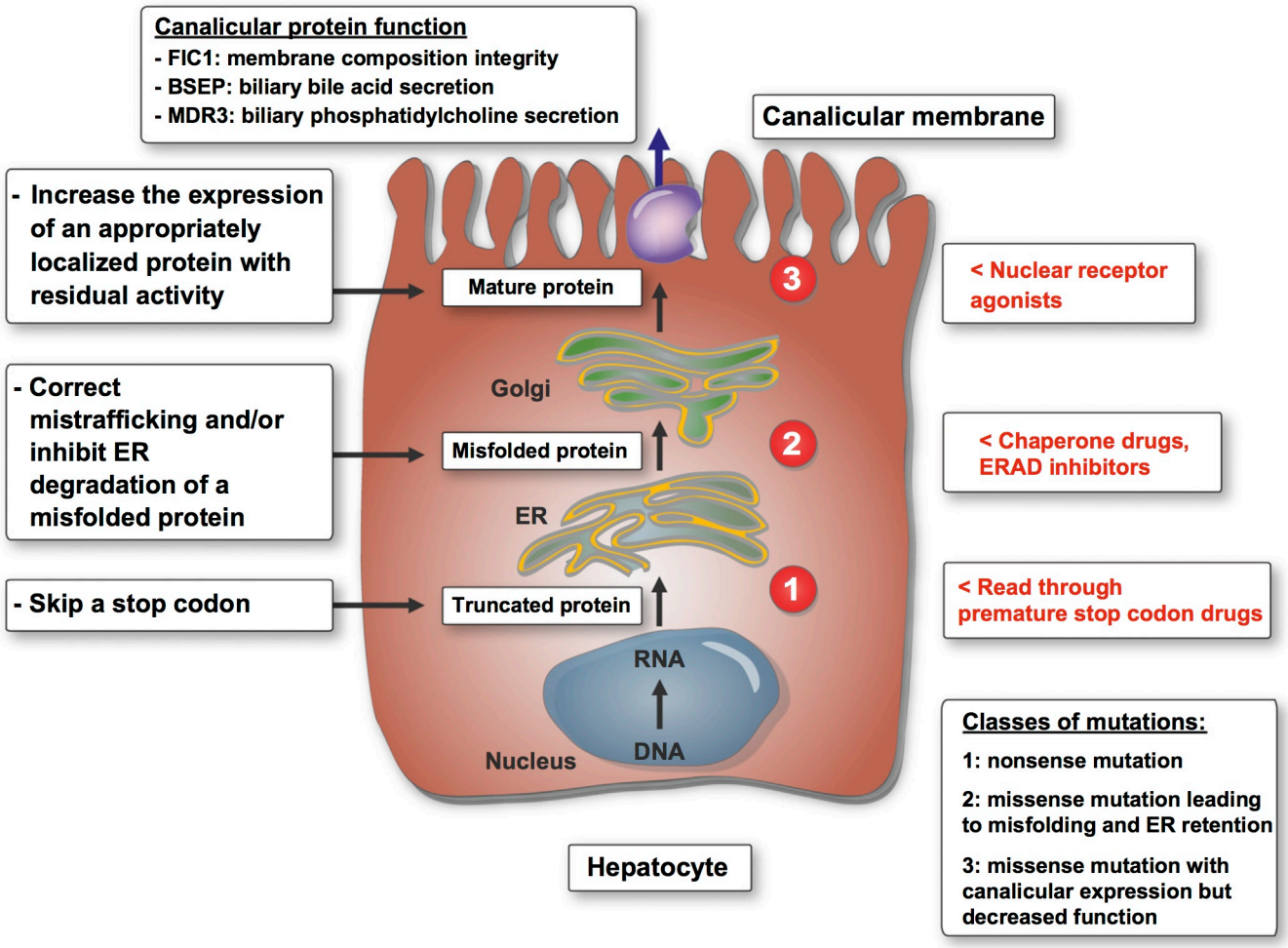
Dérivation cholécysto-colique



Exclusion iléale

Moussavi et al. Hepat Mon 2014
Van Ooteghem et al. J Hepatol 2002

PFIC/BRIC: Espoirs de Thérapie Ciblée



Gonzales et al. J Hepatol 2010

BRIC: Conclusion et Points Clés

- **Episodes récurrents de cholestase intrahépatique avec prurit sévère et GGT (sub)normale**
- **Hétérogénéité génétique: BRIC1 (ATP8B1), BRIC2 (ABCB11), autres (?)**
- **Corrélations Génotype-Phénotype (BRIC *vs* PFIC)**
- **Rares formes d'évolution péjorative (5%)**
- **Peu ou pas de traitements efficaces (rifampicine, drainage naso-biliaire, échanges plasmatiques ou MARS)**