Intermittent Intrahepatic Cholestasis of Unknown Etiology in Five Young Males from The Faroe Islands

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The syndrome of intermittent intrahepatic cholestasis was first described in two patients by *Summerskill* & *Walshe* in 1959 (1).

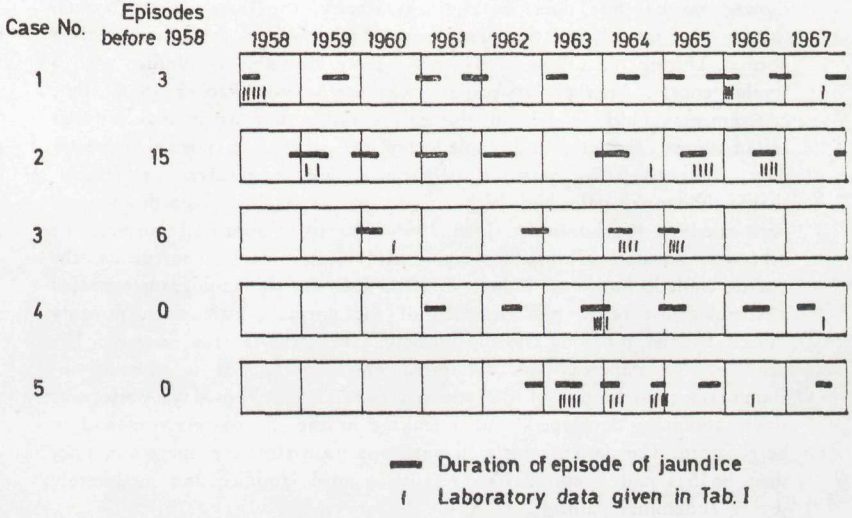
The syndrome is charachterized by: 1) several episodes of pronounced jaundice with severe pruritus and biochemical signs of cholestasis, 2) bile plugs in the liver biopsy, 3) normal intra- and extrahepatic bile ducts on direct cholangiography, 4) absence of factors known to produce intrahepatic cholestasis occasionally, as drug intake or pregnancy, and 5) symptom-free intervals of several months or years. These characteristics may be used for a definition of the syndrome, if arbitrarily at least 3 episodes of jaundice and free interval of at least 6 months are required. This will separate the syndrome from protracted and relapsing hepatitis.

Twenty-four patients with a case history concordant with this definition have been reported (1—14), inclusive the present series of five patients. Two patients from this series (case 1 and case 2) were presented in 1960 (2).

Case reports.

Case 1 (OJT) born 1942. At the age of 2 and 4 years jaundice and pruritus lasting for several months, otherwise in good health until the age of 12, when a new episode occurred, starting with sharp abdominal pain. Laparotomy Januar 1955 showed a slightly enlarged, dark, but otherwise normal-looking liver and normal extrahepatic bile ducts. No biopsy or cholangiogram was made. The pancreas was described as harder than normal. A cholecysto-gastrostomy was performed. The following episode of jaundice started when he was 15 years old, he was transferred to Rigshospitalet, Copenhagen, where laparotomy February 1958 showed slightly enlarged liver, slender bile ducts (peroperative cholangiography), normal spleen and pancreas. The gall bladder was removed. Since then repeated attacks (fig. 1),) but well-being between the attacks.

Figure I



Case 2 (EHR) born 1943. First attack 9 months old, for the following 7 years periods of jaundice of 2 to 3 months' duration once to twice a year. Laparotomy January 1950 showed macroscopically normal liver, and the bile ducts appeared normal. No biopsy or cholangiogram was made. No attacks from the age of 7 to 15 years, since then regularly jaundiced (fig. 1). During the free intervals no complaints except for food allergy.

Case 3 (HMT) born 1938. From the age of 1 to 6 years regularly jaundiced, starting each December and lasting for about 6 months. At the age of 22 years, while fishing in Greenland waters, a new episode of jaundice, starting with slight arthralgia. Laparotomy March 1960 showed a dark, but otherwise normal liver, normal extrahepatic bile ducts. No biopsy or cholangiogram. Since then 3 episodes with a typical course, except for slight arthralgia.

Case 4 (JPiD) born 1942. No jaundice or other significant disease during infancy and childhood, the first episode of jaundice occurred at the age of 19 years, laparotomy March 1961 showed normal peroperative cholangiogram, macroscopically normal liver and pancreas. Since then 5 similar episodes and perfect well-being during the intervals.

Case 5 (JML) born 1941. Normal development during infancy and childhood. The first episode of jaundice occurred at the age of 21 years, while he was fishing in Greenland waters. Laparotomy January 1963 showed normal bile ducts at cholangiography, the liver looked normal (biopsy was taken) and the pancreas was felt to be a little harder than normal. During the following 3 years 4 more episodes of jaundice with a similar course. Another laparotomy was performed October 1965, some concrements could be felt in the gall bladder, but as it was without inflammatory changes, and choledochotomy showed a normal common duct, cholecystectomy was not performed. Due to recurrent attacks of sharp abdominal pain and high urine amylase a third laparotomy was performed at Rigshospitalet June 1966. The liver appeared normal, the otherwise normal gall bladder contained 8 small, dark concrements, the ductus choledochus was slightly dilated, and the cholangiogram revealed a stenosis just below the entrance of the normal cystic duct, possibly caused by the previous choledochotomy. The stenosis was resected. The head of the pancreas was indurated and nodular, as in chronic inflammation; no biopsy of the pancreas was taken. Five days postoperatively cholascos developed, and a leakage at the site of resection had to be repaired. The patient was well until one year after the operation, since then he has had 3 episodes of relatively mild jaundice and moderately severe abdominal pain.

Family histories.

None of the patients were closely related, but great-grandfathers of case 1 and case 2 were brothers.

The occurrence of similar symptoms among the relatives of the patients was only noted in one case. The sister of case 3, born in 1942, was severely jaundiced for several months when she was 4 years old. She had been complaining of abdominal pain and itching for some time before. She was treated by bed rest at home, and no tests were made. At the age of 17 she suffered from general malaise, itching and periodically pale stools for about 6 months, followed by intense jaundice, pruritus and abdominal discomfort for about 2 months. The icteric index was 108, alkaline phosphatases 25 KA units, and alanine transaminases were normal. No liver biopsy or surgical intervention was performed, the jaundice and pruritus disappeared rather rapidly, and a cholecystogram performed shortly afterwards was normal. Since then she has had two normal pregnancies without jaundice or pruritus. She has not taken contraceptive pills.

The mother of case 5 has been jaundiced twice, once with prolonged, severe itching. Jaundice of pregnancy among the relatives of the patients has not been recorded.

Clinical findings during episodes of jaundice.

The patients were not aware of precipitating factors. As seen in fig. 1, the episodes in some cases occurred with some regularity, but no fixed seasonal pattern can be recognized. The feeding habits of the patients were unremarkable, and they did not take drugs of any kind. An episode of jaundice usually starts with fatigue, loss of appetite, nausea, and sometimes vomiting. Simultaneously or a few days later itching starts, disturbing the sleep at night. Dark urine and pale stools follows shortly afterwards, and then jaundice becomes apparent, first scleral, then universal. Constant pain centrally in the abdomen between the xiphoid process and the umbilicus without irradiation often occurs during the first week of an attack, and this is occasionally the initial symptom. In case 5 the pain usually is intense, requiring repeated injections of strong analgetics, and in case 2 it is mild or absent. In the remaining patients the pain is moderate.

The fatigue and poor appetite persist during the episode, causing a weight loss of several kilograms. Usually the first sign of remission is the return of the appetite, then some colour appears in the stools, the itching diminishes and often disappears while the jaundice still is quite marked.

During the free intervals the patients appear clinically healthy and have no specific complaints, but still they may have difficulties in re-

Table I

Case No.	Date		Serum bilirubin mg per 100 ml <1.0	Serum alanine transaminase units per ml <1.7	Serum alkaline phosphatase K-A units <10	Serum cholesterol mg per 100 ml 150—280	Serum cholesterol non-esterified mg per 100 ml 33—62	Serum albumin g per 100 ml >4.44	Serum β-globulin g per 100 ml <0.79	Urine amylase units <128	Fecal fat g per 24 h <7	Bromsulfalein retention per cent <5	Comments
1	1958	1/29	34.8	—	—	202	105	3.06	1.45	32	—	—	surgery (2/17), biopsy I
		2/25	35.2	—	—	—	—	—	—	—	48	—	
		3/28	7.2	—	—	—	—	—	—	—	—	—	
		4/25	1.7	—	—	—	—	—	—	—	—	—	
		5/28	0.3	—	—	—	—	—	—	—	—	—	
	1966	1/13	34.9	2.6	69	272	146	4.21	0.94	64	—	—	biopsy II (1/22)
		1/27	19.2	3.2	81	218	118	3.73	1.11	>1024	108	—	
		2/16	6.0	1.8	31	270	52	4.02	0.85	128	—	—	
	1967	8/22	1.7	2.5	24	216	52	4.83	0.75	256	1	26	biopsy III (8/22)
2	1959	2/4	14.9	11.0	44	—	—	3.54	1.16	—	14	—	prednisone from 3/24
		4/13	11.5	10.2	38	355	100	3.36	1.46	32	—	38	
	1964	10/16	1.1	4.2	11	184	41	4.01	0.88	—	1	6	biopsy I (10/16)
	1965	7/5	17.4	5.5	36	211	56	4 04	1.04	—	72	—	biopsy II (7/5)
		8/17	10.4	2.8	34	—	—	3.78	0.93	32	54	—	cholestyramine from 7/5
		9/14	5.0	14.0	34	132	37	4.14	0 92	—	—	—	
		10/21	1.1	8.7	22	174	25	4.32	0.80	—	10	1	
	1966	8/17	10.7	4.3	70	—	—	4.28	1.05	16	59	—	cholestyramine from 7/15
		9/13	7.8	3.2	36	—	—	—	—	—	—	—	
		10/18	2 4	6.9	24	169	51	4.47	1.14	—	32	—	
		11/4	1.2	6.8	24	—	—	—	—	—	—	—	

3	1960	7/12	1.1	1.2	17	158	39	4.60	0.55	32	2	6	biopsy I (7/12)
	1964	4/15	7.2	6.3	58	197	29	4.28	0.96	256	26	31	biopsy II (4/13)
		5/8	8.3	1.7	30	124	40	3.77	0.84	128	–	34	
		6/12	2.1	6 2	28	168	44	4.74	1.02	–	–	–	cholestyramine from 5/13
		7/17	1.0	1.4	19	145	4	5.52	0 66	–	1	4	biopsy III (7/21)
	1965	2/10	7.1	18.0	75	256	59	4.21	1.00	128	–	–	
		3/9	5.3	4.3	74	156	23	4.21	0.87	256	–	26	cholestyramine from 3/10
		3/23	2.9	13.0	48	175	33	4.53	0 89	32	–	–	
		4/20	0.8	0.7	22	154	20	4.93	0.60	32	–	–	
4	1963	11/12	16.3	7.4	49	274	97	4.27	1.07	320	24	–	prednisone from nov. 63
		11/26	13.0	2.1	38	277	100	4.24	1.03	128	–	–	biopsy II (11/21)
		12/10	6.7	13.0	31	226	34	3.39	0 94	–	–	–	
	1964	1/23	5.2	7.7	30	255	46	3.74	1.00	16	–	–	
	1967	8/11	0.4	1 5	11	199	56	4.88	0.59	256	4	10	biopsy III (8/11)
5	1963	4/16	34.4	6.2	88	199	121	3.82	1.06	> 1024	38	–	
		5/3	21.2	2.5	51	225	100	3.49	1.01	128	–	–	prednisone from 4/24
		6/6	4.8	22.0	55	263	67	4.13	0.94	–	3	–	biopsy II (6/19)
		7/5	2.1	12 0	40	–	–	–	–	16	–	6	
		8/2	2.0	3.8	44	188	55	3.94	1.01	32	–	–	prednisone until 7/20
	1964	2/12	15.9	3 0	51	250	145	3.94	0.91	32	15	–	cholestyramine from 2/20
		3/11	4.1	4.5	27	203	23	4.10	0.76	–	5	–	cholestyramine until 3/13
		4/20	0.4	2.4	22	144	13	4.25	0.61	–	–	3	biopsy III (4/14)
	1964	10/26	2.4	2.8	25	–	–	4.98	0.74	–	–	–	
		11/13	14.8	1.7	–	–	–	4.15	0.93	> 1024	10	–	
		12/21	2.3	15.0	29	–	–	4.00	0.95	16	–	–	cholestyramine from 11/14
	1965	1/18	0.7	2.0	18	–	–	4.40	0.73	–	–	–	
	1966	6/22	1.9	6.2	17	–	–	4.77	0.55	128	–	6	biopsy V (6/22)

suming their normal activities, because they fear new attacks. Most young men at the islands are fishermen, being at sea for several months at a time. All the patients had been out fishing for a period, but were unable to carry out this work.

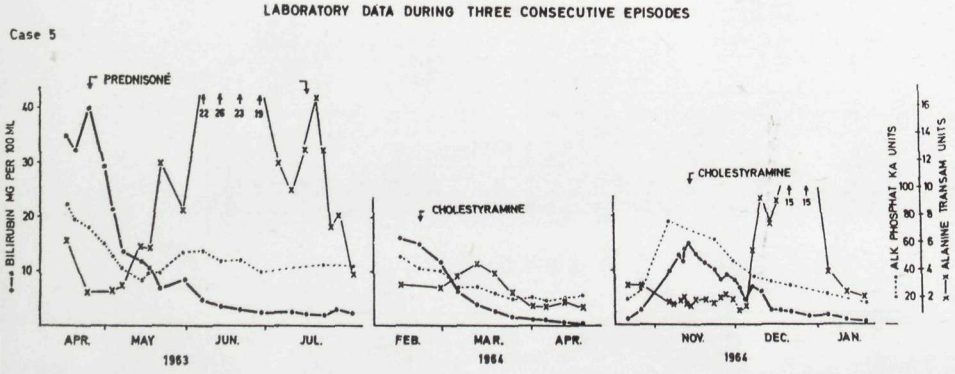
It is uncertain if abortive episodes occur. Frequently the patients have complained of periods with some fatigue, slight itching, and transitory changes in the colour of the urine and stools, but it has not been confirmed by laboratory tests. The complaints may be ascribed to an understandable anxiety regarding the possibility of the approach of a new episode of jaundice.

Laboratory findings.

The result of some selected tests at different stages are given in tab. I.

The course of the serum bilirubin (15), alkaline phosphatases (16) and alanine transaminases (17) in a typical case is shown in fig. 2. The bilirubin curve in most cases is relatively smooth. The maximum bilirubin value and the slope of the curve during recovery varies considerably from one episode to another in the same patient. The level of serum alkaline phosphatases generally follows the bilirubin curve, but becomes normal

Figure II



much later. The serum alanine transaminases are rarely excessively elevated. The highest values are constantly observed during the recovery period; often a biphasic course is found, with the lowest values during the culmination of the episode.

During the initial phases high concentrations of prothrombin-proconvertin have been found, during prolonged attacks the values may become abnormally low, but they always react promptly to treatment with vitamin K. The serum albumin (paper electrophoresis) sometimes falls to subnormal values and becomes normal during the recovery period, the γ-globulin showed a transient rise in case 5 during a severe attack, but otherwise it remains within normal limits. The α_2- and β-globulins are regularly elevated to about twice the upper normal limit and fall to normal levels during recovery.

Serum cholesterol (18) is usually elevated during the culmination of the episode and returns to normal or low values during the recovery. This is to a large extent due to changes in nonesterified cholesterol which may be lower than normal during recovery.

The BSP_{Tmax} and storage (19) and the galactose elimination capacity (20) were determined during symptom-free intervals in 4 patients (table II). In case 1 the tests were performed just prior to, and in case 2 shortly after an attack, and thus this may not represent truly "basal" values. The BSP_{max} was reduced in all, whereas BSP storage and galactose elimination only were below the normal limit in case 1.

Liver biopsies were performed at the dates given in table I and furthermore during some of the laparotomies, as mentioned in the case reports.

Table II

Quantitative Liver Tests During Free Intervals

Case No.	Normal Date	BSP Tmax mg/min 5—15*	BSP Storage mg/mg per cent 20—120*	Galactose elimination mg/min 350—700*	Serum bilirubin mg/100 ml <1.0
1	8/26/67	1.3	8	329	1.7
2	11/2/66	3.8	50	368	1.2
4	8/11/67	1.7	49	518	0.4
5	9/1/66	2.0	45	409	0.4

*)Our own determinations.

During the episodes of jaundice numerous bile plugs are found in the bile canaliculi, together with signs of moderate liver cell damage, such as a few necroses, some multinucleated liver cell, and variable stainability af the cytoplasm. The portal tracts show slight to moderate inflammatory infiltration mostly with monucleated cells, but also a few neutrophil and eosinophil granulocytes. Biopsies taken during the free intervals are essentially normal. A detailed description of the light- and electronmicroscopic-picture will be given elsehwere.

The gall bladder and bile ducts fail to visualize by cholecystography during the episodes, but they appear normal during the intervals, except for the calculi found in case 5. The increase in urine amylase usually correlates well with the abdominal pain. In case 5 pancreatic involvement was also demonstrated radiologically by retroperitoneal calcifications. Pancreas secretion studies, performed in case 1 (1965) and case 5 (1967), did not reveal decreased pancreatic function.

The EGG's were strikingly similar in all the patients, showing a negative T-wave in lead III. There were otherwise no symptoms or signs of heart disease.

Therapy.

Treatment with adrenocortical steroids and cholestyramine was tried in all patients, but due to the great spontaneous fluctuations of the disease, and the impracticability of a controlled trial, is it difficult to evaluate the effect. Neither treatment could reproducibly suppress or prevent the episodes. It is the impression of the patients, however, that steroids are without any effect, but that cholestyramine relieves the pruritus and possibly shortens the duration of the jaundice.

Discussion.

The first one or two episodes of intermittent intrahepatic cholestasis almost inevitably will be misdiagnosed as extrahepatic biliary obstruction and lead to laparotomy. When the bile ducts are found to be normal, and several similar episodes supervene, few diagnostic possibilities other than intermittent intrahepatic cholestasis will exist. The clinical picture of intermittent intrahepatic cholestasis is so characteristic and the diagnostic criteria so tangible that it is surprising that the syndrome has not been described earlier. This indicates that the syndrome is very rare or, less likely, has come into existence recently.

During the last 9 years 24 patients fulfilling the diagnostic

criteria mentioned have been reported, 18 males and 6 females. Six further cases, 5 males and 1 female, probably should be included, viz. case 2 of *de Silva et al.*[10] who only had 2 episodes of jaundice, 3 relatives to the case of *Biempica* (11, personal communication from dr. Arias), one relative to *Goldberg's* cases[14], and the sister of case 3 of this series.

The term intrahepatic cholestasis implies obstruction to the flow of bile within the liver. It is used when clinical and biochemical data are interpreted as biliary obstruction and no obstruction is found macroscopically. The lesion may be localized to the wall of the bile capillaries, i. e. in the liver cell itself, or to the intra- and interlobular bile ducts. The usual morphological examinations have not revealed the site of the lesion in intermittent intrahepatic cholestasis, but by 3-dimensional reconstruction of an interlobular bile duct in the case described by *Levy et al.*[9], obstruction by swollen cells, protruding into the lumen of the duct, were found.

The etiologic factor probably should be sought among the following categories: infection, toxic agents, and metabolic factors. Due to the unequivocal signs of liver damage during the episodes, several authors (3,6) favour the notion that it is a type of virus hepatitis. The great number of relapses in most of the patients, however, and the apparently complete restitution in the intervals is distinctly different from the usual course of viral hepatitis, and there is no positive epidemiolgic evidence to support the hypothetis. The liver cell damage can equally well be due to the effect of a toxin or to a metabolic derangement, or even to cholestasis as such[21].

An exogenic toxin as the etiologic agent could explain why several cases, as those of the present series, occur in small groups. In that case the toxin should be widely distributed, however, because the reported cases come from many parts of the world, viz. from the Faroe Islands, five from Great Britain[1,6], four from the United States[5 7 8 13], two from Belgium[3], two from Germany[4], two from Italy[14], one from France[9], one from Japan[10], one from Greece[11], and one from

Australia[12]. Some episodes in patients from the present series have started during a stay in Denmark. Dietary and other environmental toxic agents therefore are less likely. An allergic reaction has been suspected in some patients who had other allergic manifestations, e. g. case 2 of the present series and case 2 of *Kühn*[4], but no relation between these manifestations and the episodes of jaundice has been demonstrated, and in the majority of patients no symptoms or signs of allergy were found. In one patient[7] chlorpromazine and norethandrolone did not provoke jaundice, and in the present series chlorpromazine has been used as a sedative on several occasions without illeffects.

Thus by exclusion a metabolic defect may be incriminated. It is not certain whether the syndrome is heriditary. Among the 24 unquestionable cases 6 occur in three families[2 4 14] and the further six probable cases are relatives of certain cases[10 11 14], present series.

The relatively high incidence of the syndrome at the Faroe Islands (five patients among 37.000 inhabitants) conform with the hypothesis of a heriditary defect, since this community is relatively isolated with a high proportion of intermarriage. It has been suggested that the mode of inheritance is by way of a sex-linked recessive[14], but the observations are too incomplete to confirm this. The pedigrees of the probands in the present series have been followed as far as possible without revealing further cases or further links between the families of known cases. In general the families are large at the islands and the contemporary members know each other well, but in most cases only two or three generations can be traced back. It must be concluded that if the syndrome is heriditary, the dominance of the defect must be very weak.

The hepatic uptake and conjugation of bilirubin is considered to be normal[6]. Direct reacting bilirubin was found to contribute from less than 50 per cent[4 8 10 22] to about 80 per cent[11] of total bilirubin. In the patients of the present series unconjugated bilirubin was normal or lower than normal, in

case 4 and 5 the disappearance of intravenously injected unconjugated bilirubin was greater than normal, and in case 5 a considerable amount of alkali-stable monoglucuronide was demonstrated[23]. Excess formation of abnormal conjugates was suggested to be the metabolic defect of the syndrome, but too little is known about these factors in other types of cholestasis to warrant any conclusions.

Elevated bile acid concentrations in the serum has been demonstrated in several patients[8 11 14] and is presumeably the cause of the severe pruritus in all the cases[24], but detailed fractionation, especially with regard to the concentration of unconjugated lithocholic acid, have not been performed. Since this acid is capable of producing intrahepatic cholestasis and liver cell damage[25], an abnormal formation or reabsorption of lithocholic acid as the primary metabolic defect in the syndrome must be considered. This would even provide an explanation for the intermittence of the jaundice, as the cholestasis might prevent the production of lithocholic acid in the intestines for a period. The formation of gallstones in case 5 may also be related to abnormal bile acid metabolism[26].

Clinically there are many similarities between intrahepatic cholestasis of pregnancy and the present syndrome. Among the 6 female patients with intermittent intrahepatic cholestasis, the relation between pregnancy and episodes of jaundice has not been marked, since coincidence only occurred once in each of two patients[7 13]. In one patient an episode started late in a pregnancy and culminated several months after its termination[12]. Intrahepatic cholestasis of pregnancy typically recurs during al pregnancies, disappears rapidly after the delivery[27], and never occurs outside pregnancy except in some patients when treated with contraceptive pills[28]. It is felt that the evidence of a common etiology in both syndromes is meager.

The role of the pancreatitis in case 5 in the syndrome is uncertain. Three more patients in the present series had elevated urine amylase, and it is likely that the abdominal pain during the initial phases of the episodes of jaundice is due to affection

of the pancreas. Similar abdominal pain has been described in other cases[5 7 14], but generally in a milder form and without other evidence of pancreatitis. The factor which causes the cholestasis (lithocholic acid?) might also affect the pancreas, in most cases, however, to a minor degree.

In some instances prednisone[6] and cholestyramine[8 14] appears to have produced a rather dramatic improvement. The intermittence of the symptoms make the evaluation of therapy difficult, but the general impression is that these drugs are of limited value in most of the patients. If abnormal bile acid metabolism plays an etiologic role, however, the effect of bile acid sequestring therapy[29] must be further explored.

No cases have been followed for a lifetime, and the final outcome is unknown. It appears, however, that the jaundice may continue to recur even if the severity of the episodes and the duration of the free intervals may vary. It is also the impression that the recovery during the free intervals is complete, but progression to biliary cirrhosis has been suspected in one case[4] and it may be significant that the BSP storage and the galactose elimination capacity in case 1 and the BSP T_{max} of all the patients examined in this series during free intervals (case 1, 2, 4 and 5) was reduced. The extensive histochemical and electron microscopic examinations made during a free interval by *Biempica* and coworkers[11] revealed only minor residual changes, but in view of the rather substantial signs of liver cell damage during the jaundice, the risk of progressive changes cannot be ignored. When the prognosis is evaluated, it must also be taken into consideration that the patients mostly are unable to do any work during the episodes on account of general symptoms and will be more or less incapacitated even in the intervals, unless they are very long, in part perhaps due to the incertainty which the constant threat of recurrent attacks imposes. Is is therefore questionable if the word benign should be included in the designation of the syndrome[1]. From a taxonomic point of view this is superfluous, since there is no known malignant counterpart from which the syndrome must be distinguished.

Despite the clinical similarities the etiology and pathogenesis need not be the same in all the patients with the syndrome. Until this is clarified it seems preferable to use a purely descriptive designation. The term intermittent intrahepatic cholestasis is suggested because it contains the minimum and adequate information required to separate the syndrome from other types of jaundice, and because it can be directly translated into Latin which is used for official diagnoses in many countries.

SUMMARY

Clinical and biochemical findings in 5 patients from the Faroe Islands with intermittent intrahepatic cholestasis of unknown etiology are described. This brings the number of recorded cases which fulfill the suggested criteria for the syndrome to 24. The Faroe patients are all males and born between 1938 and 1943. In three patients the episodes of jaundice started during the first years of life, in two they started after puberty. Four of the patients had symptoms of pancreatic affection,, in one the diagnosis of chronic pancreatitis was confirmed by calcifications demonstrated on X-ray. Two patients are distantly related, and one patient has a sister who presumably suffers from the same disease. It is conjectured that the pathogenesis is a defect in bile acid metabolism.

ÚRTAK

Síðani 1960 eru í Føroyum kunngjørdir 5 tilburðir av einari sjáldsamari livrasjúku við ókendari atvold: Cholestasis intermittens intrahepatica. Seinastu árini eru líkir tilburðir lýstir um allan heimin, saman við hesum sjúkratilburðum í Føroyum 24 tilsamans. Allir teir føroysku eru menn, bornir í heim í tíðarskeiðinum 1938—1943. 3 av sjúklingunum fingu fyrstu ferð gulustótt fyri ársaldur og 2 fyrstu ferð eftir 14-ára aldri. Pancreas varð eisini raktur av sjúkuni og ein sjúklingur hevði eyðkenni til pancreatitis chronica. Viðvíkjandi ættarbregði er enn ógreitt. 2 av nevndu tilburðum vóru skyldir, tó ikki nær, og ein annar hevði systir, ið óivað hevur somu sjúku. Atvoldin í sjúkuni verður hildin vera brek í gallsýruevnisbroytingini.

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