IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 13, Issue 12 Ver. II (Dec. 2014), PP 09-15
www.iosrjournals.org

Study on Short Term Outcome of intrahepatic Infantile Cholestasis

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Abstract:
Background: *Outcome of infantile intrahepatic cholestasis is highly variable.*
Aim to investigate various factors affecting outcome of infantile cholestasis.
Methods: *Retrospective study was conducted through data collection of 70 infant's files who presented with intrahepatic cholestasis. They were divided into two groups according to the fate of jaundice at the end of the first year follow up. Group I: cases with persistent jaundice and group II: cases that were jaundice free by the end of the year. A comparison was done at presentation, 3 and 12 months between the two groups.*
Results: *Group I had a higher mortality and morbidity. Both groups were significantly different regards etiology, onset of jaundice, presentation to medical care, prevalence of consanguinity and pruritus. After 3 month, group I showed significant bigger and firm liver, higher ALT, AST, S.bilirubin. At 1 year, differences in weight, splenic size and S.albumin were found.*
Conclusion: *The predictive parameters of a high risk group of intrahepatic cholestasis at presentation included etiology, age of onset, positive consanguinity and itching, where at 3rd month of follow-up included big firm liver, persistently pale stool, high ALT and AST and at one year included splenomegaly and lower albumin.*
Abbreviations: *IHC- intrahepatic cholestasis, BA- bile acids, INH- idiopathic neonatal hepatitis, CMV-cytomegalovirus, IHBD- intrahepatic biliary ducts, PFIC-progressive familial intrahepatic cholestasis.*
Key Wards: *Alagille syndrome, infantile cholestasis, PFIC,*

I. Introduction

During early life, failure of bile secretion and conjugated hyperbilirubinemia are the commonest manifestations of liver dysfunction[(1)] so that jaundice is a frequent feature of early rather than late advanced liver disease as is seen in older children[(1)]. Neonatal cholestasis is defined as impaired bile formation or bile flow resulting in accumulation of biliary substances (bilirubin, bile acids and cholesterol) in blood and extrahepatic tissues [(2,3)]. It is defined biochemically as a direct bilirubin greater than 2 mg/dl or more than 20% of the total bilirubin[(4)].

Clinically, conjugated hyperbilirubinemia characterized by jaundice, acholic stool and dark urine, and hepatomegaly must always be considered as a pathological state [(5)].

The differential diagnosis of neonatal cholestasis is extensive and can be classified based on the anatomic location of pathology into extrahepatic and intrahepatic causes. Biliary atresia and choledochal cyst are examples of extrahepatic causes while common intrahepatic causes include idiopathic neonatal hepatitis, alfa 1 antitrypsin deficiency and other metabolic, infectious, chromosomal and endocrinal disorders, as well as toxic and vascular causes. Prematurity, lack of enteral feeding and medications may also result in intrahepatic cholestasis [(6)].

The prognosis of cholestasis is extremely variable ranging from a completely benign course to a progressive disease resulting in cirrhosis. It is related to the severity of complications attributable directly (effect on hepatocytes) or indirectly (transfer of bile constituents to systemic circulation and reduced delivery of bile to intestinal lumen) to diminished bile flow. The hepatocyte is the primary cell responsible for the synthesis and transport of bile acids (BA) whose flux and recirculation is the main driving force in bile formation (7). Thus it is the hepatocyte which is most likely to be damaged by bile acid retention. Bile acids are both detergent and signaling molecules which when retained within the hepatocyte lead to altered membrane composition and function, derangements of subcellular organells, and broad changes in cell signaling pathways and gene expression (8). Prolonged retention of BA within the liver leads to activation of kupffer cells and stellate cells with consequent increased expression of cytokines and progression to fibrosis (9). The hepatocytes have adaptive responses to handle cholestasis eg reduces sinusoidal import and synthesis, increases canalicular

export, and engages cytochrome p450-based xenobiotic metabolism pathways. These responses may be amenable to pharmacologic interventions which opens the way for new therapeutic tools (10).

The aim of this work was to investigate various factors (demographic, clinical, biochemical and histological) affecting outcome of infantile intrahepatic cholestasis(IHC).

II. Patients and methods

This is a retrospective study where the files of 70 infants with intrahepatic cholestasis who attended the pediatric hepatology clinics of Yassin Abdel-Ghaffar charity center for liver disease and research and Children's hospital, Ain shams University (both are tertiary referral centers) were reviewed.

Data recording and processing was done for each patient at three time points: at presentation and at 3 and 12 months from presentation, and 4 years follow up data were reviewed to record the clinical outcome for each patient. It included:

II.1 Complete history taking including time of onset of jaundice, time of presentation, parental consanguinity, similar condition in the family and perinatal history.

II.2 Physical examination including weight and height percentiles, stool color, complete abdominal examination (laying stress on the size of liver and spleen, presence of ascites and dilated abdominal wall veins), heart examination and the presence of dysmorphic features.

II.3 Investigations including:

- Complete blood picture and CRP.
- Liver function tests including the following: AST, ALT, ALT/AST, GGT, serum albumin, serum bilirubin (total, direct and total/direct) and coagulation profile (PT, PTT, and INR).
- Abdominal ultrasound.
- HIDA scan, intraoperative choalngiography: when indicated.
- Liver biopsy: if available.

II.4 Other investigations which were done for patients according to our systematic protocol:

- Alpha fetoprotein,
- Alpha 1 antitrypsin.
- T3, T4, TSH.
- Urine analysis.
- Urinary succinyl acetone.
- Serum chitotriosidase, non glucose reducing substance in urine, Serum galactose 1-p.
- Metabolic screen including urinary and plasma aminogram, carnitine and organic acids.
- TORCH screening.
- Hepatitis markers (HBsAg, HBcAb lgM,HCV Ab).
- Eye examination: both anterior and posterior segments.
- Karyotyping (for chromosomal anomalies).
- Echocardiogram, Skull X ray, Spine X ray.

According to the fate of jaundice at 12 months from presentation, patients were divided into two groups: Group 1 (with persistent jaundice) and group 2 (those who were jaundice free). The two groups were compared statistically as regards their outcome, the etiology of cholestasis, and the various demographic, clinical, biochemical, and histological parameters at presentation, 3 and 12 months from presentation.

The study protocol was approved by the hospital's ethical committees. An informed consent was obtained from the parents of the children included in the study.

III. Statistical methods

IBM SPSS statistics (V. 21.0, IBM Corp., USA, 2012) was used for data analysis. Data were expressed as Mean±SD for quantitative parametric measures in addition to Median Percentiles for quantitative non-parametric measures and both number and percentage for categorized data. Chi-square test was done to study the association between each 2 variables or comparison between 2 independent groups as regards the categorized data.

The probability of error at 0.05 was considered significant, while at 0.01 and 0.001 are highly significant.

IV. Results

Seventy patients were divided into two groups according to the fate of jaundice by the end of one year follow up, group I included 30 cases (42.8%), with jaundice, and group II included 40 cases (57.2%), who became jaundice free. A statistical comparison between the two groups was done as regards different demographic, clinical, laboratory and histological findings at different points of time (at presentation, 3months, and one year).

Table (1) shows the different etiologies of IH cholestatic patients. INH followed by low GGT cholestasis were the most common etiologies in the cohort as a whole. INH was the most common cause of jaundice in the favorable outcome group (52.5%) while only 12.5% of patients in that group were diagnosed with low GGT cholestasis. The favorable outcome group also included all those diagnosed with CMV hepatitis, trisomy 21 associated cholestasis, sepsis induced cholestasis, most of those with galactosemia (4/5) and nearly 1/2 of those with Alagille Syndrome (3/7).

Table (2) shows comparison between demographic and clinical data of group I and group II patients at presentation. Patients of group II (those who got rid of their jaundice) had an earlier onset of jaundice, presented to us at an earlier age, had lower incidence of parental consanguinity, and of itching. Although male sex& colored stools were more common findings in group II babies than those of group I, yet the difference did not reach statistical significance.

The liver was significantly bigger and firmer in group I patients and the spleen became significantly larger at one year.

No significant differences were found between the two groups as regards ALT, AST, ALT/AST, S.albumin, INR, Total bilirubin, direct bilirubin, total/direct bilirubin nor α fetoprotein at presentation. Significantly higher levels of ALT, AST, total bilirubin, direct bilirubin and lower total/direct bilirubin ratio were found in infants of group I at the 3rd month and after 1 year of follow up when compared to group II:($P<0.05$),(table 3) while a significantly lower albumin was found only after 1 year. There was no statistical difference between the 2 groups as regards the results of GGT, alkaline phosphatase nor prothrombin time ($P>0.05$) whether at presentation, 3 months or one year.

The overall outcome of patients with intrahepatic cholestasis (table 4) showed that the mortality rate in group I was 53.3% (16 patients). It was due to the following causes (liver cell failure (14), heart failure (1) and renal failure in one patient). The etiologies of these patients were INH (4), low GGT cholestasis (6), Alagille syndrome (3), galactosemia (1), and 2 miscellaneous causes (Zellweger Syndrome and Mitochondrial disorder). Progression to chronic liver disease was found in 9 cases (30%) of this group, (non syndromatic paucity of IHBD =3, low GGT cholestasis =4, INH=1 and 1 with Alpha 1 antitypsin deficiency). Liver cirrhosis was documented in 5 cases (16.7%): 4with low GGT cholestasis and 1with Alagille syndrome. One of the infants with low GGT had liver transplantation.

In group 2 (jaundice free), no deaths were reported. Eight cases (20%) developed chronic liver disease but were in stable condition [low GGT cholestasis (4 cases), INH (2 cases), Alagille syndrome (2 cases)]. Four cases (10%) progressed to liver cirrhosis (galactosemia (1), low GGT cholestasis (1), INH (1), Alagille syndrome (1)).

V. Discussion

Two thirds of cases of infantile cholestasis are due to intrahepatic causes (6). The outcome of infants with intrahepatic cholestasis (IHC) varies between complete resolution of the jaundice leaving no residual liver disease and death due to development of liver cirrhosis, portal hypertension and liver failure.

Of the 70 patients with infantile cholestasis in this study , 30 (42.8 %) were still jaundiced one year after their presentation (they formed group 1) while 40 babies (57.2%) were jaundice free by that time (group 2). Our overall 4 year survival was 77.14%. Lee et al,(11) reported a 4 year survival with native liver of 73% among 146 cases of neonatal cholestasis (29% of whom had extrahepatic biliary atresia whose survival rate was 36% .Thus 4 year survival among their cases of IHC was 87.5%; six out of the 107 survivors (4%) had liver cirrhosis. Idiopathic neonatal hepatitis (INH) was the commonest etiology (38%) in their cohort.

During our follow up 53.3% of group 1 children died, 30% developed chronic liver disease and 16.7% developed cirrhosis. On the other hand group 2 patients were all alive, most of them (70%) with no signs of chronic liver disease, 20% had chronic liver disease and 10% had cirrhosis.

From these results, it is clear that the long term outcome of babies in this study was strongly determined by the fate of jaundice one year after presentation. Bernard et al(12) stated that the long term prognosis of infants with intrahepatic cholestasis seems to be related to factors which can be recognized in the first stage of the disease. Trying to better define babies who would be expected to take the "bad prognosis "path from those who would do well we compared group 1 babies (high risk group) to group 2 ones (low risk group) at three time points: presentation, 3 months and 12 months from presentation.

A significant difference in the etiology of cholestasis was found between the two groups. In group 1 low GGT cholestasis was responsible for nearly half of the cases (46.7%) while 52.5% of babies in group 2 had INH and only 12.5% had low GGT cholestasis. At presentation, significant differences were found between both groups in the age of onset of jaundice (median of 7.5 days in group 1 vs 3 days in group 2) and age at presentation to medical care (4ms in group 1 vs 2ms in group 2). Group one babies also had a significantly higher frequency of parental consanguinity (60% vs 25%) and itching was significantly more common among them. On the other hand no significant differences were found between them as regards age, sex, gestational age, prenatal maternal history, mode of delivery, family history of a similar condition, stool color, anthropometric measures, liver or spleen examination, liver function tests nor liver histology. Bellomo et al(13) in their study on 101 infants with IHC who were classified into 3 groups: group 1 had infectious causes, group 2 had genetic-endocrine-metabolic causes and group 3 had INH found no significant differences between the three groups as regards age (age of onset of jaundice from 0- 3ms was an inclusion criterion in their study), sex, birth stature, stool color, hepatomegaly nor splenomegaly, AST, ALT, GGT, direct bilirubin nor albumin.

Progressive familial intrahepatic cholestasis (PFIC) types 1&2 and bile acid synthetic defects are the main causes of low GGT cholestasis (14). They usually start before the age of one year (often in neonatal period) and progress to cirrhosis and liver cell failure(15). They are genetic diseases that have an autosomal recessive mode of inheritance (16) and are expected to occur more commonly in offspring of consanguineous parents). In this study 14/19 (73.68%) babies with low GGT were in group 1. This explains the significant difference between groups 1 & 2 in the prevalence of consanguineous marriages. Pruritus is a dominant feature of PFIC1 and 2(14). The significantly more common itching in group 1 babies could thus be explained by the fact that 46.7% of those infants had low GGT cholestasis and 13.3% had Alagille syndrome, another cause of severe pruritus. Pruritus may not be noticed early because the neural pathways necessary for scratching wouldn't be fully developed before the age of 6 months(17,18). Group 1 babies presented at a later age than group 2 ones which could be another explanation for the higher incidence of pruritus in the former group.

INH is an entity where the causative agent (s) is unknown and may be multiple. Babies with INH usually develop jaundice in the first week of life. There are two different categories of INH with different prognoses, sporadic and familial. For sporadic cases the prognosis is very good with recovery rates in the range of 60-80% while in familial cases it is in the range of 20-40% as the cause may be a yet unidentified inborn error of metabolism or a genetic defect (19). In this study 21/26 babies with INH (80.76 %) were in the good prognosis group. The earlier age of onset of jaundice in group 2 may be accounted for by the high percentage of INH in this group.

On follow up, differences between the two groups became more apparent so that at three months the high risk group had significantly bigger and more firm liver. Their ALT, AST and total serum bilirubin were significantly higher while their total/direct bilirubin was lower. Yet the weight & height, the splenic size, serum albumin, INR and GGT were not different between the two groups. By one year of follow up the spleen became significantly bigger and the serum albumin was lower in the high risk patients. Also their weight for age percentile was significantly lower than the low risk group. INR was not different between the two groups. The progressively decreasing albumin and enlarging spleen speak for the progression of liver disease with development of portal hypertension and impaired synthetic function by four years of follow up. The low albumin could also be attributed for by the bad nutritional status of these babies as evidenced by the lower weight for age percentile. Malnutrition is common in infants with chronic hepatic diseases specially cholestasis(20). Several factors including poor intake due to anorexia and vomiting, impaired digestion and absorption of fat and fat soluble vitamins, increased caloric needs and recurrent infections may be responsible for this poor nutritional status. Additionally pancreatic insufficiency, which aggravates malabsorption, may accompany PFIC and Alagille syndrome (20,21).

Nearly 57% (4/7) of Alagille patients in our study couldn't clear their jaundice by one year of follow up. In Alagille syndrome, a dominantly inherited disorder due to mutation in JAG 1- Notch 2 , jaundice typically appears in the neonatal period and in half it is persistent resolving in later childhood (22,23).

The two babies with Trisomy 21 in this study had already cleared their jaundice by one year of follow up emphasizing the lack of association between cholestasis in that syndrome and extrahepatic biliary atresia (24)which has been reported in trisomy 18 (25). Giant cell hepatitis has also been reported in trisomy 18 (26). Recently, non cirrhotic nodular hyperplasia and severe hepatic fibrosis associated with transient myeloproliferative disorder (27,28) have been described in association with trisomy 21, raising the possibility that hepatic fibrogenesis may be due to high concentrations of growth factors derived from megakeryocytes (29). Liver biopsy was done for one of our 2 trisomy 21 patients and has revealed a picture of giant cell hepatitis.

Eighty percent (4/5) of galactosemic babies were in the low risk group. These babies were diagnosed within 1 1/2 months of age through screening of urine for non glucose reducing substance and diagnosis

confirmed by a high galactose one phosphate in red blood cells. Milk & milk products were eliminated from diet and replaced by Lactose free milk.

It is to be noted that in this study like in most others (13, 30, 31, 32, 33, 12) INH was the commonest cause of IHC (26/70 - 37.1 %). Low GGT cholestasis was more frequent in our study compared to others. This could be explained by the high percentage of parental consanguinity (28/70 - 40 %) especially in group 1(18/30 - 60%).

Thus a high risk group of IHC defined by etiology (low GGT), later age at onset, later age at presentation, parental consanguinity and having pruritus can be recognized at presentation and further confirmed at three months of follow up by presence of an enlarged firm liver, elevated ALT, AST, S bilirubin and lower total / direct bilirubin.

Table (1): Etiology of cholestasis in group I and group II

Etiology	**Total No=70**	**%**	**Groups**				**X2**	**P**
			Group I (no=30) :persistent jaundice		**Group II (no=40) :jaundice free**		24.932	0.002*
			N	%	N	%		
INH	26	37.1%	5	16.7%	21	52.5%		
Low GGT cholestasis	19	27.1%	14	46.7 %	5	12.5%		
Alagille syndrome	7	10%	4	13.3%	3	7.5%		
Galactosemia	5	7.1%	1	3.3%	4	10%		
CMV+ve hepatitis	3	4.2%	0	0.0%	3	7.5%		
Non syndromic paucity of IHBD	3	4.2%	3	10%	0	0.0%		
Trisomy 21	2	3%	0	0.0%	2	5%		
Neonatal sepsis	1	1.4%	0	0.0%	1	2.5%		
Combined etiology	1	1.4%	0	0.0%	1	2.5%		
Miscellaneous	3	4.2%	3	10%	0	0.0%		
Total	70	100%	30	100%	40	100%		

* Significant

Miscellaneous causes were: mitochondrial disorder; zellweger syndrome, alpha 1 antitrypsin deficiency

Combined etiology: CMV and low GGT Cholestasis.

Table (2): comparison between group 1 and group 2 as regards demographic and clinical data at presentation

History		**Group I (30)**		**Group II (40)**		**Z**	**P**
		Median	**IQR**	**Median**	**IQR**		
Age at onset (days)		7.5	57.25	3	8.75	-2.22	.026*
Age at presentation (days)		122.5	147	60	110.75	-3.06	.002*
		Group I (30)		**Group II (40)**		**X2**	**P**
		N	**%**	**N**	**%**		
Sex	Male	16	53.3%	29	72.5%	2.743	0.098
	Female	14	46.7%	11	27.5%		
Gestational age	Full term	26	86.7%	30	75%	1.458	0.227
	Preterm	4	13.3%	10	25%		
Maternal disease	Positive	3	10%	2	5%	0.646	0.421
	Negative	27	90%	38	95%		
Maternal drugs	Positive	1	3.3%	1	2.5%	0.043	0.836
	Negative	29	96.7%	39	97.5%		
Mode of delivery	Vaginal	22	73.3%	30	75%	0.025	0.875
	Cesarean	8	26.7%	10	25%		
Family history of similar condition	Positive	8	26.7%	6	15%	1.458	0.227
	Negative	22	73.3%	34	85%		
Consanguinity	Positive	18	60%	10	25%	8.750	0.003*
	Negative	12	40%	30	75%		
Stool color	Clay	16	53.3%	13	32.5%	3.066	0.080
	Normal	14	46.7%	27	67.5%		
Itching	Positive	13	43.3%	4	10%	10.359	0.001*
	Negative	17	56.7%	36	90%		

*Significant

Table (3): Comparison between group I (persistent jaundice) and group II (Jaundice-free) as regards investigations (liver function tests)

Investigations		**Group I (30)**		**Group II (40)**		**Z**	**P**
		Median	**IQR**	**Median**	**IQR**		
Albumin (g/dL)	at presentation	3.90	0.87	4.10	0.90	-1.12	0.26
	3rd month	3.95	0.57	4.10	0.80	-0.91	0.37

	1 year	2.90	1	4.20	1	-2.47	0.01*
Total Bilirubin (mg%)	at presentation	10.05	8.20	10.67	7.15	-0.06	0.95
	3rd month	8.90	8.90	1.00	0.90	-5.71	0.00*
	1 year	7.15	12.63	0.55	0.63	-4.51	0.00*
Direct Bilirubin (mg%)	at presentation	7.16	5.59	6.31	7.23	-0.87	0.38
	3rd month	6.65	7.85	0.50	0.87	-5.38	0.00*
	1 year	6.10	9.70	0.27	0.39	-3.89	0.00*
Tbil/Dbil	at presentation	1.458	0.51	1.662	0.48	-1.68	0.09
	3rd month	1.387	0.32	2.100	1.47	-3.59	0.00*
	1 year	1.330	0.54	2.592	1.06	-3.30	0.001*
ALT (U/L)	at presentation	165.00	179.50	97.50	145.75	-0.78	0.44
	3rd month	141.00	156.00	49.00	64.00	-4.08	0.00*
	1 year	84.00	55	28.00	16	-4.43	0.00*
AST (U/L)	at presentation	223.50	307	143.50	333	-0.25	0.80
	3rd month	221.00	344.50	76.50	50.00	-4.10	0.00*
	1 year	131.00	67	47.00	10	-3.98	0.00*
ALT/AST	At presentation	0.680	0.30	0.642	0.42	-0.20	0.84
	3rd month	0.634	0.30	0.761	0.44	-1.59	0.11
	1 year	0.675	0.33	0.588	0.16	-0.55	0.58
ALP (U/L)	at presentation	722.00	1145.00	674.00	533.00	-0.18	0.86
	3rd month	608.00	1977.00	533.50	635.50	-0.67	0.50
GGT (U/L)	at presentation	64.00	282	79.00	132	-0.84	0.39
	3rd month	40.00	198.00	34.50	136.75	-0.70	0.48
	1 year	64.00	130.00	15.50	73.00	-1.33	0.18
INR	At presentation	1.1	0.13	1.2	0.30	-1.34	0.18
	3rd month	1.2	0.42	1.12	0.12	-1.08	0.28
	1 year	1.17	0.21	1.04	0.29	0.59	0.56
α feto-protein		540	4601.5	890	4803.5	-0.69	0.49

*Significant

Table (4): The clinical outcome of cases at 4 years of follow up (no=70)

Outcome	**Group (30)**	**Group II (40)**	**X2**	**P**
Death	16 patients (53.3%)	No deaths (0.0%)	43.632	0.000*
Chronic liver disease without cirrhosis	9 patients (30%)	8 patients (20%)		
Liver cirrhosis	5 patients (16.7%)	4 patients (10%)		
No signs of chronic liver disease	0 patients (0%)	28 patients (70%)		

*Significant

VI. Conclusion

The predictive parameters of unfavorable outcome of intrahepatic cholestasis at presentation included etiology, age of onset, positive consanguinity and itching, where at 3rd month of follow-up included big firm liver, persistently pale stool, high ALT and AST and at one year included splenomegaly and lower albumin.

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