Biliary Atresia: GGT vs histopathology as diagnostic tool

ABSTRACT:

Back ground: Biliary Atresia (BA) also known as "progressive obliterative cholangiopathy" is one of the most common conditions requiring pediatric liver transplant and the most common surgically treatable cause of neonatal cholestasis. Associated malformations are present in 25% of cases and it is most common in East Asia, with incidence reported as high as one in 5,000. BA presents with cholestatic Jaundice, initially indistinguishable from physiological jaundice. Symptoms include progressive cholestasis, causing yellowing of the skin, pruritis, pale stools, dark urine. **METHODS:** This study is a Cross sectional study conducted at the Department of Pediatric Medicine, The Children's Hospital & Institute of Child's Health, Lahore in the duration of 6 months (2018-2019), after approval from the Institution's Review Board. All patients of age ≤ 14 months, presenting in pediatric emergency with cholestatic jaundice and fulfilling inclusion criteria were included in this study. **RESULTS:** In our study a total of 150 cases were enrolled. The mean age of patients in months was 7.13 ± 3.81. The male to female ratio of the patients was 1.3:1, 86(57.33%) males and 64(42.67%) females. The results showed that the mean initial observation of jaundice was 8.54 ± 3.89 days with minimum and maximum duration of 2 & 15 days, respectively. In our study the mean GGT level of the patients was 303.13 ± 58.53. In our study, on the basis of GGT level BA was diagnosed positive in 83 cases and negative in 67 cases, which was exceptionally consistent with the gold standard i.e. histopathology which diagnosed 82 cases as positive for BA and labelled 68 cases negative.

CONCLUSION: Serum GGT elevated levels are suggestive of biliary atresia

Key Words: Atresia, GGT, Jaundice

INTRODUCTION:

Biliary Atresia (BA) also known as "progressive obliterative cholangiopathy" is one of the most common conditions requiring pediatric liver transplant. [1] BA is characterized by obliteration or discontinuity of the extrahepatic biliary system, resulting in bile flow obstruction. Associated malformations are present in 25% of cases which include polysplenia, preduodenal portal vein, malrotation, absence of Inferior Vena Cava, cardiac anomalies, intrapulmonary shunting, asplenia, pancreatic anomalies and Situs Inversus. [2] Polysplenia constitute 10-50% of these associated anomalies. [3] BA is most common in East Asia, with incidence reported as high as one in 5,000. [4] Patients with biliary atresia can be subdivided into 2 distinct groups: those with isolated biliary atresia (postnatal form), which accounts for 65-90% of cases, and patients with associated situs inversus or polysplenia/asplenia with or without other congenital anomalies (fetal/embryonic form), comprising 10-35% of cases. [5]

In the case of biliary atresia, most infants are full-term, although a higher incidence of low birthweight may be observed. The low birth weight and pre-term population is prone to develop jaundice and may further hinder judgment of treating physician. [6,7] There is no known cause of biliary atresia, however viral infection and autoimmune theories have been proposed. [8,9] [10] However, experimental evidence is insufficient to link any of these theories to the etiology of biliary atresia.

BA presents with cholestatic Jaundice, initially indistinguishable from physiological jaundice which is usually harmless, and rarely persists beyond 2 weeks thus warranting evaluation beyond this period as also part of the NASPGHAN guideline for cholestasis. [11] Symptoms of BA are evident between one to six weeks after birth with progressive cholestasis, causing yellowing of the skin, pruritis, pale stools, dark urine. [10,12]

The disorder represents the most common surgically treatable cause of cholestasis encountered during the newborn period. If left untreated, progressive fibrosis and biliary cirrhosis with portal hypertension will develop in children who do not drain bile eventually leading to liver failure. [1,10] [13] Hepatocellular carcinoma may be a risk for patients with cirrhosis. The only effective treatments are surgeries

such as the Kasai procedure and liver transplantation. Bile flow, even if achieved at surgery, may be inadequate in as many as one third of patients necessitating early liver transplantation i.e. before 2 years. [13] [14]

Multiple laboratory studies are performed for BA including Serum bilirubin (total and conjugated), Alkaline phosphatase (AP), gamma-glutamyl transpeptidase (GGT), serum aminotransferases, serum bile acids. [10] Other investigations are performed as well. These include ultrasonography which can exclude specific anomalies of the extrahepatic biliary system particularly choledochal cysts but is highly observer dependent and Hepatobiliary Iminodiacetic Acid (HIDA) scan which provides unequivocal evidence of intestinal excretion of radiolabel confirming patency of the extrahepatic biliary system but has diminished reliability at very high conjugated bilirubin levels (>20 mg/dL). [15]

Other more invasive tests for BA include Duodenal intubation and duodenal string test which are cumbersome, time-consuming, as well as unreliable and Endoscopic retrograde cholangiopancreatography (ERCP) however its use is widely limited due to unavailability of side-viewing instruments for neonates. [15] The final confirmatory test are percutaneous liver biopsy and per-operative cholangiogram. However is percutaneous liver biopsy is considered as the gold standard for diagnosis of BA with reported sensitivity and specificity of 88.2% as well diagnostic accuracy as high as 93% to 94%. [10,12,16,17]

Among the laboratory tests Conjugated hyperbilirubinemia is always an abnormal finding and must always raise suspicion for BA. [18] GGT is an integral membrane protein of the bile canaliculus and elevated serum GGT activity can be found in diseases of the liver, and biliary system particularly in cholestatic conditions thus has significance as a diagnostic marker. [19] GGT levels closely correlate with ALP levels and are increased in all biliary obstructive conditions. In general, ALP is still the first test for biliary disease. The main value of GGT over ALP is in verifying that ALP elevations are, in fact, due to biliary disease since ALP can also be increased in certain bone diseases, whereas GGT levels are almost invariably determined only by liver and bile duct disorders. Although any single laboratory tests alone cannot accurately discriminate between biliary atresia and the other causes of neonatal cholestasis, they are much less invasive and are relatively cheap

and safe. Often important tests such as GGT are omitted and their combined role might be a possible explanation for lack of individual importance.

METHODS:

This study is a Cross sectional study, designed to assess the diagnostic accuracy of Gamma-Glutamyl Transpeptidase (GGT) in the diagnosis of Biliary Atresia, conducted at the Department of Pediatric Medicine, The Children's Hospital & Institute of Child's Health, Lahore in the duration of 6 months (2018-2019), after approval from the Institution's Review Board. All patients of age ≤ 14 months, who presented in pediatric emergency with cholestatic jaundice were included in this study. All patients with choledochal cyst and/or any malignant hepatic condition, (as per medical record), were excluded from the study.

RESULTS:

In our study a total of 150 cases were enrolled. The mean age of patients in months was 7.13 ± 3.81. The male to female ratio of the patients was 1.3:1, 86(57.33%) males and 64(42.67%) females. The results showed that the mean initial observation of jaundice was 8.54 ± 3.89 days with minimum and maximum duration of 2 & 15 days, respectively. In our study the mean GGT level of the patients was 303.13 ± 58.53. (**Table#1**). In our study, on the basis of GGT level BA was diagnosed positive in 83 cases and negative in 67 cases, which was exceptionally consistent with the gold standard i.e. histopathology which diagnosed 82 cases as positive for BA and labelled 68 cases negative. (**Table#2**).

Table -1: Demographic parameters of study patients

Descriptive Statistics	Mean	Std. Deviation	Minimum	Maximum
AGE (months)	7.13	3.806	1	14
JAUNDICE FIRST OBSERVED (days)	8.54	3.896	2	15
GGT level (U/L)	303.13	58.531	200	400
GENDER	**COUNT**		**PERCENTAGE**	
MALE	86		57.33%	
FEMALE	64		42.67%	

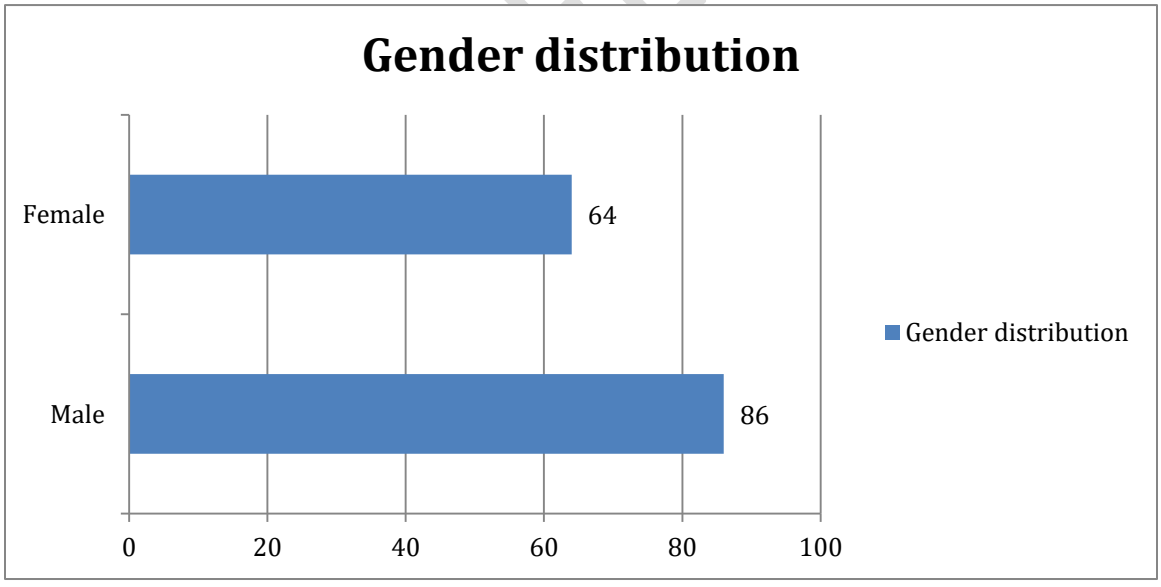

Fig-1:Gender distribution in study participants

Table -2: Chi-squre comparison between GGT and histopathology

BA on GGT	BA on Histopathology		Total	Chi-square	p-value
	Positive	Negative			
Positive	75	8	**83**	**95.535**	**<0.0005**
Negative	7	60	**67**		
Total	**82**	**68**	**150**		

DISCUSSION:

Biliary atresia is the result of a destructive, idiopathic inflammatory process which affects intra- and extrahepatic bile ducts, leading to fibrosis and obliteration of the biliary tract, eventually leading to biliary cirrhosis. It occurs worldwide, with prevalence as high as 1 in 5,000 live births in Asia and is the most frequent indication for pediatric liver transplant [4].

GGT has long been sought out to be used in diagnosing BA and differentiating it from NH. One of the earlier studies include a study by Wright and Christie, who established the role of serum GGT as a useful discriminant in differentiating between BA and NH. [20] Studies that subsequently followed supported its role however, they were either statistically insignificant partly due to small sample size or were not able to identify the role of GGT as an independent test. With a sample size of 150 cases our study was by far the largest to prove the role of GGT test in the diagnosis of biliary atresia.

In our study the mean value of GGT level (U/L) of the cases was 303.13 with a standard deviation of 58.53. Literature varies on the exact value of GGT diagnostic for BA however most authors agree on GGT level ≥ 300 U/L as diagnostic for biliary atresia. A study conducted in Taiwan used GGT level ≥ 300 U/L as diagnostic criterion to differentiate BA from Neonatal Hepatitis (NH) demonstrated appreciable sensitivity of 83%, specificity of 92% and diagnostic accuracy of 85%. [21] A study corelating GGT values with BA according to age reported sensitivity and specificity of 66.7% and 70.5%, respectively however there sample was incomparably small. [22] Another study conducted in Taiwan observed unsatisfactory diagnostic accuracy however they reported a specificity of 98.1% for GGT levels ≥ 300 U/L. [23]

The current gold standard for diagnosis of biliary atresia is histopathological examination of Liver Biopsy specimen, with reported diagnostic accuracy as high as 94%. [10,12,16,17] We have therefore kept it as our standard too and analyzed the GGT test results against biopsy results. The data in our study was statistically significant with a p-value <0.0005 and yielded the sensitivity of GGT as 91.46% with specificity of 88.24%, NPV of 89.55%, PPV of 90.36% and the diagnostic accuracy of 90%. These results were very promising and congruent with similar studies performed elsewhere.

CONCLUSION:

Serum raised GGT levels has suggestive role in the diagnosis of biliary atresia

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