

ORIGINAL ARTICLE

^{99m}Tc-labelled hepatoiminodiacetic acid (HIDA) scintigraphic evaluation of prevalence of biliary atresia in children with persistent neonatal jaundice: a comparison with national, regional & international studies

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Abstract

Aims This retrospective study aimed at determining the prevalence of biliary atresia in children presenting with persistent neonatal jaundice by technetium-99m labelled hepatoimino diacetic acid (^{99m}Tc-HIDA) scintigraphy. The results were compared with those from similar studies conducted in Pakistan, South East Asia & internationally.

Methods The study was conducted at Nuclear Medicine Centre, Armed Forces Institute of Pathology, Rawalpindi, from June 2010 to December 2012. A total of 80 patients with persistent neonatal jaundice were included in the study with 54 males & 26 females in a ratio of about 2 to 1. Main outcome measure was demonstration of biliary atresia on technetium-99m labelled hepatoiminodiacetic acid (^{99m}Tc-HIDA) scan.

Results Patients with a clinical diagnosis of persistent neonatal jaundice were included in the study. The mean age for males and females at presentation was 224 & 122 days respectively. Biliary atresia was diagnosed in 45 patients with 28 being male and 17 female patients respectively.

Conclusion A significant percentage of patients (56.25%) presenting with persistent neonatal jaundice are found to have biliary atresia on scintigraphic evaluation.

Key words: *^{99m}Technetium-labelled hepatoiminodiacetic acid (HIDA) scan, biliary atresia.*

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Introduction

Neonatal mortality rate is the most conspicuous indicator of population-based health services in any country. 130 million infants are born each year worldwide, out of whom 4 million die in the first 28 days of life. Two-thirds of these deaths occur in just 10 countries in Asia, with Pakistan bearing the third highest burden of neonatal mortality. With around 300,000 deaths annually and a neonatal mortality rate of 49/1000, Pakistan

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Pakistan has 7 % share of neonatal deaths globally [1].

In the absence of population-based studies, the etiological basis of most neonatal deaths is often not identified in time. Among other neonatal illnesses, persistent neonatal jaundice has a significantly poor prognosis with about 40% mortality [2]. Persistent neonatal jaundice that lasts more than 21 days may occur in up to 15 % of all new born with an underlying unconjugated hyperbilirubinaemia [3]. Discriminating between life-threatening conjugating hyper bilirubinaemia and unconjugating jaundice in the early stage can be difficult. The importance of having a correct diagnosis at that time is emphasised by the possibly fatal outcome associated with missed, delayed or incorrect diagnosis. Biliary atresia is the single commonest cause of neonatal liver disease with conjugated hyperbilirubinemia, with less than 10% survival by third year of life in the absence of surgical rescue. An early diagnosis of biliary atresia can thus be of life-saving consequence [4].

Data on the prevalence of biliary atresia among patients with persistent neonatal jaundice in Pakistan is scanty. This is further compounded by the relatively low sensitivity and subjective error in utilizing ultrasonography for diagnosis. HIDA is an expensive diagnostic utility not freely available except at specialist centres but its high negative predictive value (almost 100%) can help in triaging the patients with persistent neonatal jaundice for diagnosing biliary atresia versus other causes of neonatal jaundice.

This study was carried out at the Nuclear Medical Centre, AFIP, Rawalpindi, in order to determine the prevalence of biliary atresia in children presenting with persistent neonatal jaundice using technetium-labelled hepato iminodiacetic acid (^{99m}Tc-HIDA) scintigraphy. The results were compared with those of other studies carried out nationally, regionally and internationally.

Materials and Methods

The patients were referred for HIDA scanning to the Nuclear Medical Centre, AFIP, from various hospitals of Rawalpindi/Islamabad and adjoining areas and other tertiary care hospitals from upper part of the country. The study only included those patients referred with a clinical diagnosis of persistent neonatal jaundice, if the jaundice exceeded 21 days with no amelioration on phototherapy.

The preparation for the test included cessation of breastfeeding for at least 4 hours before the test. A 2 mCi dose of ^{99m}Tc-DISIDA with was injected intravenously. Anterior abdominal 60-sec images were obtained at 1-min, 5-min, 10-min, 15-min, 30-min, 1-hour, 2-hour, 3-hour and 24-hour postinjection and where appropriate, additional delayed views were obtained to optimise visualisation of radionuclide intestinal transit. Three nuclear medicine physicians visually analysed the scintigrams. Main outcome measure was demonstration of biliary atresia as exhibited by persistent retention of ^{99m}Tc-DISIDA in the hepatobiliary conduits with absent visualization of activity transit in gallbladder and intestines till 24 hours.

Results

A total of 80 patients with persistent neonatal jaundice were included in the study. The patients were selected on a retrospective analysis of patient records over a 3-year period and new patients with persistent neonatal jaundice were also included in the study. There were 54 males and 26 females in the study with a ratio of about 2 to 1. The mean age for males and females at presentation was 224 and 122 days respectively. The age range for males and females was 20-295 and 30-700 days respectively.

Scintigraphic diagnosis of biliary atresia was made in 56.25% (45/80) patients (28 of 54 males and 17 out of 26 female patients). The

Table 1 *Comparison with national, regional and international studies*

S No	Author(s)	Year	Place of study	Type of Study	Pts with neonatal jaundice (number)	Pts with biliary atresia (number)	Pts with biliary atresia (percentage)	*p*-Value*
Studies from Pakistan								
1	Present Study	2013	Pakistan	Retospective and cross sec	80	45	56.25	-
2	Omer M et al	2010	Pakistan	Retrospective	35	3	8	<0.0001
3	Ahmed M et al	2006	Pakistan	Retrospective	62	39	62.9	0.35
4	Mirza TM et al	2010	Pakistan	Retrospective	100	41	41	0.12
Studies from India								
1	Poddar U et al	2009	India	Prospective	101	35	35	0.01
2	Poddar U et al	2004	India	Retrospective	51	20	39.2	0.14
3	Shah I et al	2012	India	Retrospective	46	28	60.9	0.55
Studies from Iran								
1	Majd M et al	1980	Iran	Prospective	22	10	45.4	0.65
Studies from South East Asia								
1	Kanegawa et al	2003	Japan	Retrospective	55	29	52.7	0.95
2	Lin WY et al	1992	Taiwan	Prospective	66	15	22.7	0.0002
3	Lee WS et al	2010	Malaysia	Prospective and cross sec	146	35	24	<0.0001
International Studies								
1	Gilmour SM et al	1997	Canada	Retrospective	86	40	47	0.43

** 2-tailed p-value was calculated by mid Fischer exact test with a p-value of less than 0.05 considered significant*

male-to-female ratio was 1.6 to 1. The prevalence of biliary atresia in male and female patients with persistent neonatal jaundice was 51.8% (28/54) and 65.3% (17/26) respectively. The age range of male and female patients diagnosed with biliary atresia was 20 to 180 and 39 to 180 days respectively. The mean age for males and females at presentation was 74.5 and 100 days respectively.

We compared our results with the results of three studies each from Pakistan and India and one study each from Iran, Taiwan, Malaysia, Japan and Canada.

Discussion

In the present study, the percentage of patients with biliary atresia out of those presenting with persistent neonatal jaundice was 56.25%. The percentage of patients with biliary atresia out of those presenting with persistent neonatal jaundice in all studies ranged from 8% to 62.9%. In the four studies from Pakistan including the present study, the percentage of patients with biliary atresia ranged from 8% to 62.9% thus showing a very high disparity in reported prevalence [5-7]. For studies from the same region, this is quite

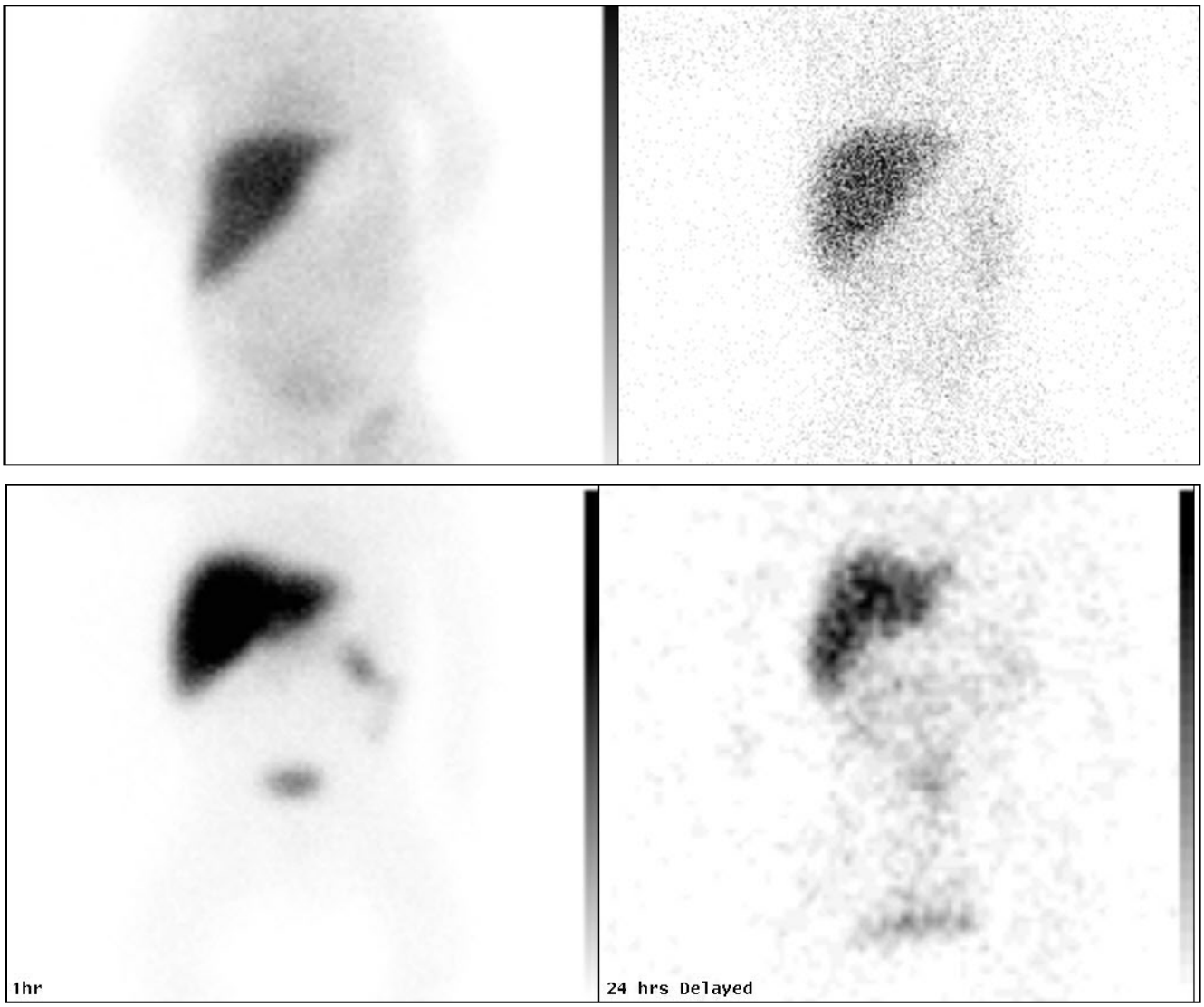

Figure 1 *HIDA scan showing absence of gut excretion in patient with biliary atresia (top) as compared to a patient with hepatic parenchymal impairment without biliary atresia (bottom)*

a significant difference in prevalence of biliary atresia. Our results show a statistically significant difference in the prevalence of biliary atresia in patients with persistent neonatal jaundice compared with the reported incidence quoted by Omer *et al.* (56.25% *vs.* 8%; $p < 0.0001$) in their study (see Table 1). However, on the other hand the reported incidence was not significantly different (56.25% vs. 62.9%; $p = 0.35$, 53.7% *vs.* 41%; $p = 0.12$) between our study and the results of studies by Ahmed *et al.* and Mirza *et al.* respectively [6, 7]. The fact that statistically significant differences were only observed with one study out of four from Pakistan, highlights the possible effects of non-representative sampling, small sample size, low sensitivity of diagnostic modality as well as subjective observer bias in the study by Omar *et al.* [5].

In the three studies from India, the percentage of patients with biliary atresia ranged from 35% to 60.9% [8-10]. The results of these studies were comparable to ours and statistically significant difference was

only seen with one study by Poddar *et al.* (56.25% *vs.* 35%; p=0.01) [Table 1]. This suggests that the prevalence of biliary atresia in patients with persistent neonatal jaundice is approximately the same in the Indo-Pak region as shown in five out of seven studies from this region.

In the study from Iran, the prevalence of biliary atresia was 45.4%, which was comparable to the prevalence seen in most of the other studies from the Indo-Pak region [11]. We also compared our results with one study each from Malaysia, Taiwan and Japan [12-14]. The prevalence of biliary atresia in the study from Japan was 52.7% and the difference was not statistically significant as compared to our present study (56.25% *vs.* 52.7%; p = 0.95). However, our results differed significantly from those reported in the studies from Malaysia and Taiwan with a lower percentage of patients identified with biliary atresia in both studies (56.25% *vs.* 22.7%; p=<0.0001, 56.25% *vs.* 24%; p=0.0002). These differences should be borne out in further studies from those areas with more patient numbers. It could actually represent an underlying demographic difference in disease burden between Pakistan, Malaysia and Japan, with a higher prevalence of biliary atresia in the patients from Pakistan presenting with persistent neonatal jaundice. Finally, we compared our results with those of a study reported from Canada and the differences were not significant (56.25% *vs.* 47%; p = 0.43) [15].

Biliary atresia is a significant underlying aetiology in up to 41% to 62.9% of Pakistani patients with neonatal jaundice. The paediatricians, physicians, neonatologists, radiologists and nuclear medical specialists should have a high index of suspicion for biliary atresia in such cases. Any other diagnosis should only be considered after the possibility of biliary atresia has been effectively ruled out by adequate histopathologic, radiologic or scintigraphic evidence to the contrary. The use of diagnostic modalities with a high negative predictive value such as scintigraphy is of primary value in reaching such a diagnosis.

Conclusion

Biliary atresia is a fairly common cause of persistent neonatal jaundice: seen in 56.25% cases of neonatal jaundice. Persistent elevation of liver enzymes in the neonatal period despite phototherapy should caution the paediatrician and neonatologist alike to the possibility of this underlying aetiology. The significant risk associated with delay in correct diagnosis of this condition warrants an early and timely recourse to highly sensitive diagnostic modalities like HIDA scintigraphy in patients where there is a high index of suspicion.

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