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The Utility Value of Pre-laparotomy Diagnostic Parameters in the Differential Diagnosis of Infantile Cholestasis

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Summary

Akinyinka OO, Faweya AG, Sodeinde O. The Utility Value of Pre-laparotomy Parameters in the Differential Diagnosis of Infantile Cholestasis. *Nigerian Journal of Paediatrics* **1998; 25: 10.** In order to evaluate the usefulness of simple pre-laparotomy parameters in differentiating intrahepatic cholestasis (IHC) from extrahepatic cholestasis (EHC), 27 infants with cholestatic jaundice were studied prospectively. On initial evaluation, the following data was collected: birthweight, age at observation of jaundice, presence and consistency of hepatomegaly, splenomegaly, direct serum bilirubin, alkaline phosphatase, haematocrit, prothrombin time, peroxide haemolysis test and duodenal intubation and aspiration test. The sensitivity, specificity, negative and positive predictive values of each parameter were determined, while the definitive diagnosis was confirmed by exploratory laparotomy and intra-operative cholangiography in 12 cases of the clinical course of the disease. Patients with EHC reported to hospital late while the presence of acholic stools within 10 days of admission, hepatomegaly of >3 cm, peroxide haemolysis of >80 percent lysis and/or the presence or absence of bilious fluid on duodenal aspiration aided differential diagnosis of infantile cholestasis in the infants. The specificity of acholic stools, hepatomegaly and duodenal aspiration tests was 73.3 percent, 66.7 percent and 93.3 percent respectively, while the corresponding negative predictive values were 78.6 percent, 100 percent and 100 percent, respectively. These simple parameters in a set-up with limied diagnostic facilities, experience and expertise, should encourage immediate exploratory laparotomy, wedge liver biopsy and intraoperative cholangiography.

Introduction

PERSISTENT cholestasis in the infant is univeral with a reported incidence of 1:2500 live births in South-east England.[1] Although no true incidence studies among Nigerian infants have been published, many cases with diverse aetiology have been reported.[2,3] Most cases of persistent cholestasis result from intrahepatic diseases[2,4] which generally require medical management. Conversely, cases due to extrahepatic diseases most commonly result from biliary atresia[2-5] which requires corrective surgery within 10 weeks of birth for significantly improved long term prognosis.[6,7] Thus, the need for early diagnosis and appropriate intervention becomes evident. Due to considerable overlap of results of investigations, no single diagnostic test accurately differentiates intrahepatic disease from extrahepatic cholestasis.[2-13] Although ^{99}Tc - IDA(iminodiacetic acid) scans have considerably improved discrimination of the two groups of diseases, the procedure is not available in Nigeria. Alagille,[8] utilising four clinical observations comprising birthweight, age at onset of acholic stools, stool colour within 10 days of admission and evidence of liver involve-

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ment, demonstrated 82 percent discrimination. This power of discrimination was only marginally improved by liver histology.[8]

In the diagnostic work-up of patients with cholestatic jaundice, especially in a hospital setting with limited diagnostic facilities, early discrimination by simple diagnostic criteria is important. In an effort to establish simple and easily available criteria for such early discriminants in Nigerian infants, the present study was designed to evaluate the relative usefulness of some clinical, laboratory and investigative parameters in the differential diagnosis of infantile cholestasis.

Table 1

Clinical and Laboratory Data in Children with Extrahepatic and Intrahepatic Cholestasis

Data	*Extrahepatic Cholestasis*		*Intrahepatic Cholestasis*		*P values*
	N	*Mean ± SD (Range)*	*N*	*Mean ± SD (Range)*	
Age when jaundice was observed (days)	12	20.3 ± 15.1 (2-60)	15	19.2 ± 28.8 (1-84)	NS
Birth weight (kg)	10	2.95 ± 0.51 (2.1-3.6)	11	2.78 ± 0.80 (1.61-4.36)	NS
Liver size(cm) below right costal margin in mid-clavicular line	12	6.1 ± 1.4 (4-8)	15	3.1 ± 1.7 (0-7)	<0.001
Total serum bilirubin (mg/dl)	12	15.1 ± 8.3 (8.8-38.8)	15	28.2 ± 25.3 (9.6-57.6)	NS
Direct serum bilirubin (mg/dl)	12	11.1 ± 5.0 (6.4-28.8)	15	13.8 ± 9.4 (5.4-32.0)	NS
Alkaline phosphatase (KA units/dl)	10	81.3 ± 20.9 (60-117)	10	74.6 ±38.0 (27-146)	NS
Haematocrit (%)	12	30 ± 6 (25-33)	15	29 ± 5 (25-40)	NS

NS = Not significant

Patients and Methods

Twenty-seven consecutive infants suffering from infantile cholestasis seen at the University College Hospital, Ibadan, were enrolled into the study. On enrolment, each infant was examined and the following data were recorded: the age at presentation in hospital, birthweight, stool colour within 10 days of admission, liver size and consistency, while any evidence of splenic enlargement was noted. Laboratory investigations carried out in each case included: total and direct serum bilirubin, alkaline phosphatase, peroxide haemolysis test,[9] prothrombin time, haematocrit, and total and differentials of white cell counts and blood cultures to confirm or exclude bacteral sepis as the cause of conjugated hyperbilirunbinaemia. Furthermore, all the 27 patients underwent duodenal intubation and aspiration test[3] after five days pre-treatment with phenobarbitone to aid choleresis. The twelve patients who did not drain bilious fluid on duodenal aspiration, were surgically explored and the biliary tree delineated by intra-operative cholangiography.

The data obtained were analysed statistically by EPI-INFO version 6, using chi-square test, Student 't' test and the exact binomial test, where relevant. Sensitivity, specificity and negative predictive values were determined using 2 x 2 contingency tables. Statistical differences at five percent levels were regarded as significant. Sensitivity in this study was defined as the ability of a specific test to identify correctly, those individuals who truly had extrahepatic obstruction while specificity was the ability of a test to identify correctly, those individuals who did not have extrahepatic obstruction.

Results

Twelve of the 27 patients did not drain bilious fluid on duodenal aspiration; all the 12 were confirmed to have extrahepatic biliary atresia at laparotomy with intra-operative cholangiography demonstrating the level of biliary tree obstruction. The remaining 15 patients suffered from intrahepatic cholestasis which subsequently improved. Five of the 15 cases of intrahepatic cholestasis had bacterial sepsis on blood culture, while no aetiological factor was demonstrable in

the remaining 10. The male: female ratio among those with biliary atresia was 1.4:1 while for intrahepatic cholesasis, it was 2.4:1.

Table II

Comparison of Clinical and Laboratory Data (expressed as percentages) in Extrahepatic (EHC) and Intrahepatic Cholestasis (IHC).

	EHC (n = 12)	*IHC (n = 15)*	*P values*
Acholic stools within 10 days of admission	75	27	<0.05
Hepatomegaly ≥ 3cm	100	33	<0.001
Hard consistency of liver	50	10	<0.05
Normal consistency of liver	50	90	<0.05
Splenomegaly	67	73	NS
Anaemia	42	40	NS
Leucocytosis	25	33	NS
Prothrombin time ratio >1.5secs	50	40	NS
Peroxide haemolysis test >80%	80	33	<0.05

NS = Not significant

Table 1 shows that although there was considerable overlap in the features evaluated, patients suffering from intrahepatic diseases reported earlier in hospital at a mean age of 8.5 weeks ± 5.3 compared with 16.3 weeks ± 7.7 in those suffering from biliary atresia (P <0.005). The liver was significantly larger (P <0.001) in infants with biliary atresia with a mean (±SD) of 6.1cm (± 1.4) compared with the 3.1 cm (±1.7) in those with intrahepatic cholestasis. However, no significant differences (P >0.05) were demonstrated with regard to mean birthweight, age at onset of jaundice, level of serum bilirubin, level of alkaline phosphatase and prothrombin times (Tables 1 and 11).

Table II shows that significantly higher proportions of infants with biliary atresia than those with intrahepatic cholestasis had acholic stools within 10 days of admission, hepatomegaly of hard consistency and peroxide haemolysis test of >80 percent lysis (P <0.05). Hepatomegaly of >3cm and non-bilious aspirate were the most sensitive at 100 percent each, while the age at onset of jaundice was the least sensitive among the indices evaluated as to their discriminatory value (Table III). Similarly, hepatomegaly of ≥ 3cm and non-bilious aspirate demonstrated the highest negative predictive value, while age of jaundice showed the lowest negative predictive values (Table III).

Table III

Discriminant Statistics at 95% Confidence Interval (CI) in evaluating Infantile Cholestasis

	Sensitivity (%)	*Specificity (%)*	*PPV (%)*	*NPV (%)*
Acholic stools within 10 days of admission	75 (42.8-93)	73.3 (44.8-91.1)	69.2 (38.9-89.6)	78.6 (48.8-94.3)
Hepatomegaly ≥ 3cm	100 (69.9-100)	66.7 (38.7-87.0)	70.6 (44.0-88.6)	100 (65.5-100)
Splenomegaly	66.7(35.4-88.7)	26.7 (8.9-55.2)	42.1 (21.1-66.0)	80 (44.2-96.5)
PHT > 80%	80 (44.2-96.5)	66.7 (35.4-88.7)	66.7 (35.4-88.7)	80 (44.2-96.5)
Age at onset of jaundice (days)	16.7 (2.9-29.1)	40 (17.5-67.1)	18.2 (3.2-52.2)	37.5 (16.3-64.1)
PT ratio > 1.5 seconds	50.0 (22.3-77.7)	60 (32.9-82.5)	18.2 (22.3-77.7)	60 (32.9-82.5)
Duodenal aspiration test	100 (69.9-100)	93.3 (66.0-99.7)	92.3 (62.1-99.6)	100 (73.2-100)

Figures in parentheses represent values at 95% CI

PT = Prothrombin time

PHT = Peroxide haemolysis test

PPV = Positive predictive value

NPV = Negative predictive value

Discussion

Distinguishing intrahepatic diseases from extrahepatic cholestasis is a diagnostic challenge because early surgical intervention within 10 weeks of life in infants with biliary atresia improves quality of survival.[5,8] In order to achieve early diagnosis, many clinical and laboratory parameters [5,8,14-17] have been evaluated for their discriminatory properties in differentiating biliary atresia from intrahepatic disease. Alagille, [5,8] using simple clinical parameters such as stool colour within 10 days of admission, birthweights, age at observation of jaundice and clinical features of liver involvement, have shown that correct differentiation of extrahepatic cholestasis from intrahepatic cholestasis was possible in 82 percent of cases. In the present study where patients reported late for health care and in the context of limited facilities and experience, we studied the utility value of clinical and investigative parameters on first contact with infants presenting with cholestatic jaundice in order to evaluate their usefulness in differentiating biliary atresia from neonatal hepatitis and therefore, aid early and appropriate intervention.

The generally late presentation of the patients in hospital may be related to the relatively late observation of jaundice through the dark skin of people of African descent compared with caucasians. Despite this, there was still a significant difference in the times the two types of cases presented, the time of presentation in hospital being shorter in infants with intrahepatic diseases than those with extrahepatic cholestasis. The differences may be due to the fact that infants suffering from neonatal hepatitis appeared to be generally more ill than those with extrahepatic obstruction who are otherwise healthy and so, jaundice was of less concern.

Although Alagille [5,8] in his study, observed that the mean birthweight of infants with neonatal hepatitis was significantly lower than that of infants with biliary atresia, the present study as well as another study from the same institution [2] did not demonstrate such differences in the mean birthweights of both groups. At the time of presentation in this study as well as in others, [5,8] liver size and consistency were sufficiently discriminatory.

In the present series as in many others, the utility of laboratory parameters is usually limited as there is considerable overlap.[10-14] Serum direct reacting bilirubin and alkaline phosphatase [10,14] are only markers of cholestasis and the serum levels in both groups were similar and therefore, not discriminatory. Whitington,[15] in his search for simple diagnostic tools in the differential diagnosis of infantile cholestasis, suggested that elevated serum alkaline phosphatase and gamma glutamic transpeptidase (GGTP) may be discriminatory.

However, due to lack of adequate resources, it was not possible to assess the utility of these enzymes in the present study. The peroxide haemolysis test[3] which is an indirect measurement of the extent of absorption of vitamin E, was sufficiently discriminatory in the present series, with haemolysis of red cells in biliary atresia much higher than in neonatal hepatitis. This finding may be a reflection of the differences in the duration and severity of malabsorption of vitamin E. Our centre relies heavily on duodenal intubation and aspiration test, which is relatively simple and shows considerable specificity, sensitivity and accuracy.[3] False negative results of non-bilious duodenal aspirate in severe intrahepatic disease may however result from complete cessation of bile flow. Therefore, pre-treatment with choleretics such as phenobarbitone is used to reduce this error.[16] An earlier study had demonstrated a sensitivity of 100 percent and specificity of 93.3 percent for duodenal aspiration.[3] Liver biopsies which have an accuracy of 85-95 percent [17,18] in differentiating biliary atresia from neonatal hepatitis are sometimes associated with complications, and are best carried out in specialised centres. Furthermore, the utility of histology is often limited by the delay in obtaining the results of findings in our centre. Therefore, the insistence of prelaparotomy liver biopsy and histology report further delays appropriate intervention in a patient already late in presenting to hospital.

In view of the diagnosic constraints often encountered by health workers in developing countries, it is recommended that in the diagnostic workup of infantile cholestasis, the combination of the presence of acholic stools, peroxide haemolysis test of >80 percent lysis and evidence of liver involvement, should suggest the immediate need for exploratory laparotomy, intraoperative cholangiogram and wedge biopsy.

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