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Etiological Spectrum of Chronic Liver Disease in Infants and Children: A Histopathology-Based Clinicopathological Analysis.

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Abstract

Background: Chronic liver disease (CLD) in the paediatric population differs fundamentally from that in adults, both in its causes and in its natural history. The aetiological spectrum is wide, strongly age-dependent, and includes a substantial proportion of treatable and potentially reversible conditions. Liver biopsy remains central to establishing a definitive diagnosis, particularly in the non-cirrhotic stages, yet histopathology-based series from the Indian subcontinent are limited. ***Objectives:*** To determine the aetiological spectrum of chronic liver disease in infants and children on the basis of liver histopathology, to describe the clinical and biochemical profile of each aetiological category, and to assess the concordance between the pre-biopsy clinical diagnosis and the final histopathological diagnosis. ***Methods:*** A cross-sectional observational study was conducted in the Department of Pathology in collaboration with the Department of Paediatrics of a tertiary care teaching hospital over a period of two years. One hundred consecutive children aged from birth to 18 years with clinical, biochemical or radiological evidence of chronic liver disease of more than six months' duration, who underwent percutaneous liver biopsy, were enrolled. Biopsies were processed routinely and examined with haematoxylin and eosin along with a panel of special stains (Masson trichrome, reticulin, periodic acid–Schiff with and without diastase, Perls, orcein and rhodanine) and immunohistochemistry (HBsAg, CK7, CK19) as indicated. Necroinflammatory activity and fibrosis were graded and staged by the METAVIR system. Data were analysed using IBM SPSS Version 21.0; the chi-square test was applied to categorical variables and Cohen's kappa to assess clinicopathological agreement, with $p<0.05$ taken as significant. ***Results:*** Of 100 children, 34 were infants (≤12 months) and 66 were older than one year, with a male-to-female ratio of 1.38:1. Jaundice (78%) and hepatomegaly (71%) were the commonest presenting features. Considered as a whole, biliary and cholestatic disorders formed the largest aetiological group (23%), followed by metabolic and genetic disorders (21%), autoimmune hepatitis (13%), infective causes (12%) and cryptogenic disease (10%). The distribution was strongly age-dependent: extrahepatic biliary atresia (12%) and idiopathic neonatal hepatitis (8%) dominated infancy, whereas Wilson disease (14%) and autoimmune hepatitis (13%) were the leading causes beyond one year and Wilson disease was the single commonest aetiology overall. Established cirrhosis (METAVIR F4) was present in 25% of biopsies. Histopathology confirmed the clinical impression in 68 cases, refined or altered it in 24, and was non-contributory in 8 ($\kappa = 0.61$). ***Conclusion:*** The aetiological spectrum of paediatric chronic liver disease is broad and shifts markedly with age, from obstructive and cholestatic disorders in infancy to metabolic and autoimmune disease in later childhood. Liver biopsy, supported by a targeted panel of special stains and immunohistochemistry, altered or refined the working diagnosis in almost a quarter of cases and retains a decisive role in the evaluation of these children, a substantial proportion of whom have treatable disease.

Keywords: Chronic liver disease, children, liver biopsy, histopathology, biliary atresia, Wilson disease, autoimmune hepatitis, aetiological spectrum.

INTRODUCTION

Chronic liver disease is defined as a continuing inflammatory or cholestatic process of the liver persisting for more than six months, culminating, if unchecked, in progressive fibrosis, architectural distortion and cirrhosis.[1] In children it constitutes a clinically distinct entity rather than a younger version of the adult disease. Alcohol and chronic viral hepatitis, which together account for the majority of adult cases, contribute comparatively little in the paediatric setting, where inherited metabolic defects, developmental anomalies of the biliary tree and immune-mediated injury predominate.[2] This distinction is not merely academic. A substantial proportion of paediatric aetiologies are treatable, and several—Wilson

disease, autoimmune hepatitis, galactosaemia, tyrosinaemia and extrahepatic biliary atresia among them—carry outcomes that depend critically on the interval between presentation and diagnosis.[3,4]

The single most important organising principle in this field is age at presentation. In the first year of life, chronic hepatic injury presents almost invariably as neonatal cholestasis, a syndrome affecting approximately one in every 2500 live births, within which extrahepatic biliary atresia and the monogenic intrahepatic cholestatic disorders account for the majority of cases.[5] Biliary atresia alone remains the commonest indication for paediatric liver transplantation worldwide, and the success of the Kasai portoenterostomy falls sharply when the procedure is undertaken beyond 60 to 90 days of life, so that the diagnostic window is measured in weeks.[6,7] Beyond infancy the spectrum changes character entirely: metabolic disorders, chief among them Wilson disease, autoimmune liver disease, chronic viral hepatitis and, increasingly, non-alcoholic fatty liver disease come to the fore.[8,9]

Reports from the Indian subcontinent have consistently documented a spectrum distinct from that of Western series. Wilson disease is disproportionately represented, being reported as the commonest cause of non-cirrhotic chronic liver disease in children in some Indian centres, at a frequency considerably higher than that described in Europe or North America.[10,11] Conversely, the historically important entity of Indian childhood cirrhosis has all but disappeared following the decline in the use of brass and copper vessels for infant feeding, illustrating how the local aetiological profile evolves with changing environmental exposures.[12] Even within India the adult spectrum documented by multicentric survey bears little resemblance to the paediatric one,[13] and hospital-based paediatric series from different regions differ appreciably among themselves.[14] Such regional variation means that spectrum data generated elsewhere cannot be transposed uncritically to Indian practice.

Against this background, liver biopsy occupies a pivotal position. Non-invasive serology, imaging and biochemistry will identify the cause in many children, but a considerable residue remains in which the diagnosis is either unresolved or misattributed. Histopathology permits the direct recognition of pattern-defining features—ductular reaction and bile plugs in large duct obstruction, giant cell transformation in neonatal hepatitis, interface hepatitis with plasma cells in autoimmune disease, ductopenia in Alagille syndrome, and periodic acid–Schiff-diastase-resistant globules in alpha-1 antitrypsin deficiency—and simultaneously provides the stage of fibrosis, which carries prognostic weight independent of aetiology.[15,16] Its role has been questioned by authors who argue that careful clinical assessment can obviate the procedure in a majority of children,[10] making the actual diagnostic yield of biopsy a question worth measuring rather than assuming.

The present study was therefore undertaken to define the aetiological spectrum of chronic liver disease in infants and children on a histopathological basis, to correlate the morphological findings with the clinical and biochemical profile, and to quantify the extent to which liver biopsy modified the pre-biopsy clinical diagnosis.

MATERIALS AND METHODS

Study design and setting: This was a cross-sectional, observational, hospital-based study conducted in the Department of Pathology in collaboration with the Departments of Paediatrics and Paediatric Gastroenterology of a tertiary care teaching hospital over a period of two years. The study protocol was reviewed and approved by the Institutional Ethics Committee before commencement, and written informed consent was obtained from a parent or legal guardian of every participant, with additional assent obtained from children above the age of seven years.

Inclusion criteria: Consecutive children from birth to 18 years of age with clinical, biochemical, radiological or endoscopic evidence of chronic liver disease of more than six months' duration, in whom a percutaneous liver biopsy was performed as part of the diagnostic evaluation, were enrolled. Infants with conjugated hyperbilirubinaemia persisting beyond 14 days of life were included under the operational category of neonatal cholestasis, irrespective of the six-month criterion, in keeping with prevailing guidance.[5]

Exclusion criteria: Children with acute liver failure, acute self-limiting hepatitis, isolated unconjugated hyperbilirubinaemia or hepatic malignancy were excluded, as were those in whom biopsy was contraindicated by uncorrectable coagulopathy (INR >1.5 after vitamin K), platelet count <60 000/mm³, gross ascites or a suspected vascular lesion. Specimens containing fewer than five portal tracts were excluded from staging but retained for descriptive analysis.

Clinical and laboratory evaluation: A structured proforma recorded age of onset, symptom duration, perinatal history, consanguinity, family history of liver disease or unexplained sibling death, and drug exposure. Examination documented jaundice, stool and urine colour, organomegaly, ascites, pruritus, dysmorphism, anthropometry and slit-lamp examination for Kayser–Fleischer rings. Investigations comprised complete blood count, liver function tests, prothrombin time with INR, viral markers (HBsAg, anti-HCV, anti-HAV IgM, anti-HEV IgM), serum ceruloplasmin with 24-hour urinary copper

interpreted by the Ferenci score where Wilson disease was suspected,[17] autoantibody profile (ANA, anti-smooth muscle antibody, anti-LKM-1) with serum IgG, serum alpha-1 antitrypsin, metabolic screening where indicated, abdominal ultrasonography with Doppler, and upper gastrointestinal endoscopy where portal hypertension was suspected. A provisional clinical diagnosis was recorded by the treating paediatric gastroenterologist before biopsy and sealed for later comparison with the histological diagnosis.

Biopsy procedure and processing: Ultrasound-guided percutaneous liver biopsy was performed under sedation using a 16- or 18-gauge automated cutting needle, targeting a minimum core length of 15 mm. Specimens were fixed in 10% neutral buffered formalin, processed routinely and sectioned at 4 µm. All cases were stained with haematoxylin and eosin, Masson trichrome, reticulin and periodic acid–Schiff with and without diastase digestion; Perls Prussian blue, orcein and rhodanine were applied for iron and copper-associated protein. Immunohistochemistry for HBsAg was performed where viral serology was positive, and CK7 and CK19 to assess ductular reaction and enumerate interlobular bile ducts where paucity was suspected.

Histopathological assessment: Slides were reported independently by two pathologists blinded to the sealed clinical diagnosis, with discordance resolved by joint review. Portal and lobular inflammation, interface hepatitis, ductular reaction, bile duct proliferation or loss, cholestasis, giant cell transformation, steatosis, ballooning and storage material were recorded semiquantitatively, and fibrosis was staged by the METAVIR system (F0–F4),[18] with the Ishak system applied in parallel to the chronic hepatitis cases.[19] The final aetiological diagnosis integrated the histological pattern with clinical, biochemical and radiological data.

Statistical analysis: Data were analysed in IBM SPSS Version 21.0. Continuous variables are expressed as mean ± standard deviation and categorical variables as frequencies and percentages. The chi-square or Fisher exact test was used for categorical comparisons, the independent t-test for continuous variables, and Cohen's kappa for clinicopathological agreement. A p-value <0.05 was considered significant.

RESULTS

One hundred children who underwent liver biopsy for chronic liver disease during the study period were analysed. The mean core length was 14.6 ± 3.2 mm with a mean of 8.4 ± 2.7 portal tracts per section, and 92 specimens met the adequacy criterion. Four children developed minor complications (transient pain in three, self-limiting hypotension in one); no major complication or procedure-related death occurred.

Table 1: Age and sex distribution of the study population (n=100)

Age group	Male	Female	Total (%)
≤12 months (infants)	19	15	34 (34%)
>1–5 years	15	11	26 (26%)
>5–12 years	17	11	28 (28%)
>12–18 years	7	5	12 (12%)
Total	58 (58%)	42 (42%)	100 (100%)

Infants constituted the largest single age group, accounting for slightly more than a third of the cohort, which reflects the concentration of neonatal cholestasis within the first year of life. A male preponderance was evident across all age bands, with an overall male-to-female ratio of 1.38:1, consistent with previously reported paediatric series.

Table 2: Clinical presentation of the study population (n=100)

Clinical feature	Infants (n=34)	Children >1 year (n=66)	Total (%)
Jaundice	32	46	78 (78%)
Hepatomegaly	28	43	71 (71%)
Splenomegaly	9	35	44 (44%)
Failure to thrive / growth failure	21	17	38 (38%)
Ascites / abdominal distension	8	23	31 (31%)
Pale or clay-coloured stools	24	5	29 (29%)
Pruritus	12	10	22 (22%)
Upper gastrointestinal bleeding	1	13	14 (14%)
Neurological / Kayser–Fleischer ring	0	9	9 (9%)
Hepatic encephalopathy	1	5	6 (6%)

Jaundice and hepatomegaly were the dominant presenting features in both age strata. The distinguishing features between the two groups were, however, informative: pale stools and failure to thrive clustered strongly in infancy, pointing towards

obstructive and cholestatic pathology, whereas splenomegaly, ascites and variceal bleeding were far commoner beyond the first year, indicating that older children more often presented after portal hypertension had already supervened. Neurological manifestations and Kayser–Fleischer rings were confined entirely to children above five years of age.

Table 3: Laboratory parameters at presentation (mean ± SD)

Parameter	Infants (n=34)	Children >1 year (n=66)	p-value
Total bilirubin (mg/dl)	9.8 ± 4.6	4.2 ± 3.9	<0.01
Conjugated bilirubin (mg/dl)	6.4 ± 3.1	2.3 ± 2.4	<0.01
AST (U/L)	186 ± 94	142 ± 118	0.06
ALT (U/L)	148 ± 82	164 ± 132	0.52
Alkaline phosphatase (U/L)	642 ± 288	384 ± 176	<0.01
Gamma-glutamyl transferase (U/L)	312 ± 204	118 ± 96	<0.01
Serum albumin (g/dl)	3.2 ± 0.6	3.0 ± 0.7	0.16
INR	1.3 ± 0.3	1.4 ± 0.4	0.20

Infants demonstrated a markedly cholestatic biochemical profile, with significantly higher total and conjugated bilirubin, alkaline phosphatase and gamma-glutamyl transferase than older children. Transaminases, by contrast, did not differ significantly between the groups, and neither did albumin or INR, indicating that the pattern rather than the magnitude of biochemical derangement carried the age-related discriminatory value.

Table 4: Aetiological spectrum by diagnostic category (n=100)

Diagnostic category	Number	Percentage
Biliary and cholestatic disorders	23	23%
Metabolic and genetic disorders	21	21%
Autoimmune hepatitis	13	13%
Infective (viral) causes	12	12%
Cryptogenic / undetermined	10	10%
Idiopathic neonatal hepatitis	8	8%
Non-alcoholic fatty liver disease	6	6%
Fibropolycystic disease	5	5%
Vascular disorders	2	2%
Total	100	100%

Grouped by broad category, biliary and cholestatic disorders formed the largest block, closely followed by metabolic and genetic disease. Together these two categories accounted for 44% of the cohort. Autoimmune and infective causes contributed a further quarter, while a cryptogenic label persisted in one in ten children despite full evaluation including histology.

Table 5: Individual aetiologies stratified by age group (n=100)

Aetiology	≤12 mo	>1–5 y	>5–12 y	>12–18 y	Total
Extrahepatic biliary atresia	12	0	0	0	12
Idiopathic neonatal hepatitis	8	0	0	0	8
Progressive familial intrahepatic cholestasis	4	2	0	0	6
Paucity of ducts / Alagille syndrome	3	0	0	0	3
Choledochal cyst	2	0	0	0	2
Neonatal CMV infection	2	0	0	0	2
Galactosaemia / tyrosinaemia	2	0	0	0	2
Wilson disease	0	3	8	3	14
Autoimmune hepatitis	0	4	6	3	13
Chronic hepatitis B	0	3	4	1	8
Chronic hepatitis C	0	0	2	0	2
Glycogen storage disease	0	4	0	0	4
Alpha-1 antitrypsin deficiency	0	1	0	0	1
Congenital hepatic fibrosis	0	3	2	0	5
Non-alcoholic fatty liver disease	0	0	3	3	6
Budd–Chiari syndrome	0	2	0	0	2
Cryptogenic / undetermined	1	4	3	2	10
Total	34	26	28	12	100

This table constitutes the principal finding of the study. The aetiological profile is sharply age-partitioned: every case of extrahepatic biliary atresia, idiopathic neonatal hepatitis, ductal paucity, choledochal cyst, neonatal cytomegalovirus infection and the disorders of carbohydrate and amino acid metabolism presented within the first year, whereas Wilson disease, autoimmune hepatitis, chronic viral hepatitis and fatty liver disease were encountered exclusively beyond it. Extrahepatic biliary atresia was the commonest single aetiology in infancy (12 of 34, 35.3%), while Wilson disease was the commonest beyond infancy (14 of 66, 21.2%) and, taken across the whole cohort, the commonest single diagnosis overall (14%). Progressive familial intrahepatic cholestasis straddled the boundary, two of the six cases presenting after the first birthday.

Table 6: Principal histopathological features observed (n=100)

Histological feature	Number	Percentage
Portal inflammation	84	84%
Lobular inflammation	57	57%
Portal / bridging fibrosis	51	51%
Ductular reaction	46	46%
Cholestasis (canalicular / hepatocellular)	41	41%
Interface hepatitis	39	39%
Bile plugs in ductules	33	33%
Established cirrhosis	25	25%
Macrovesicular steatosis	24	24%
Bile duct proliferation	21	21%
Multinucleate giant cell transformation	19	19%
Hepatocyte ballooning	17	17%
Plasma cell-rich portal infiltrate	15	15%
Mallory–Denk bodies	8	8%

Portal inflammation was near-universal and therefore of little discriminatory value. The pattern-defining features were more instructive: bile duct proliferation with bile plugs and portal oedema was seen in 11 of the 12 cases of biliary atresia, giant cell transformation was concentrated in infancy and was the dominant feature of idiopathic neonatal hepatitis, and a plasma cell-rich interface hepatitis characterised the autoimmune group. Cirrhosis was already established in a quarter of the cohort at the time of first biopsy, underscoring late presentation.

Table 7: Stage of fibrosis by METAVIR system (n=100)

Fibrosis stage	Infants (n=34)	Children >1 year (n=66)	Total (%)
F0 – no fibrosis	3	3	6 (6%)
F1 – portal fibrosis without septa	8	10	18 (18%)
F2 – portal fibrosis with few septa	9	15	24 (24%)
F3 – numerous septa without cirrhosis	9	18	27 (27%)
F4 – cirrhosis	5	20	25 (25%)

Advanced fibrosis (F3 and F4 combined) was present in 52% of the cohort. The burden fell disproportionately on older children, among whom 38 of 66 (57.6%) had F3 or F4 disease compared with 14 of 34 (41.2%) infants, a difference that reflects both the longer duration of subclinical injury and the tendency of metabolic and autoimmune disorders to remain silent until architectural damage is well advanced.

Table 8: Diagnostic yield of special stains and immunohistochemistry

Stain / marker	Performed	Contributory	Principal diagnostic use
Masson trichrome	100	100	Staging of fibrosis
Reticulin	100	96	Architecture, nodularity
PAS with diastase	100	5	A1AT globules (1), glycogen storage (4)
Orcein / rhodanine	100	12	Copper-associated protein, Wilson disease
Perls Prussian blue	100	5	Iron overload
CK7 / CK19	34	29	Ductular reaction, duct paucity
HBsAg immunohistochemistry	26	8	Confirmation of chronic hepatitis B

Masson trichrome and reticulin were universally informative for staging and architecture. Among the aetiology-specific stains, orcein and rhodanine gave the highest yield, demonstrating copper-associated protein in 12 cases and supporting the

diagnosis of Wilson disease; it should be noted that a negative copper stain does not exclude the diagnosis, particularly in the pre-cirrhotic stage where copper distribution is uneven. Cytokeratin immunohistochemistry proved decisive in distinguishing ductular reaction from true bile duct proliferation and in confirming the three cases of ductal paucity.

Table 9: Concordance between pre-biopsy clinical diagnosis and final histopathological diagnosis (n=100)

Outcome of biopsy	Number	Percentage
Histopathology confirmed clinical diagnosis	68	68%
Histopathology refined or altered the diagnosis	24	24%
Histopathology non-contributory / inconclusive	8	8%

Overall agreement between the sealed pre-biopsy clinical diagnosis and the final histopathological diagnosis was substantial (Cohen's $\kappa = 0.61$). Biopsy nevertheless refined or overturned the working diagnosis in almost a quarter of children. The commonest such reassignments were from a clinical label of idiopathic neonatal hepatitis to extrahepatic biliary atresia and vice versa (7 cases), from cryptogenic cirrhosis to Wilson disease or autoimmune hepatitis (6 cases), and from suspected chronic hepatitis to congenital hepatic fibrosis (3 cases). The eight non-contributory biopsies comprised six inadequate cores and two in which non-specific changes precluded a definite aetiological assignment.

DISCUSSION

This histopathology-based analysis of 100 children with chronic liver disease demonstrates an aetiological spectrum that is broad, regionally characteristic and, above all, sharply stratified by age. The male preponderance (1.38:1) and the predominance of jaundice and hepatomegaly at presentation accord closely with the Indian series of Dhole et al, who reported a 60% male preponderance and jaundice with abdominal distension as the leading complaints in 55 children.[20] The finding that infancy is dominated by obstructive and cholestatic disease, with extrahepatic biliary atresia accounting for 35.3% of infantile cases, is consistent with the joint NASPGHAN–ESPGHAN estimate that biliary atresia underlies 25–40% of neonatal cholestasis.[5] The clinical importance of this figure lies in its time-dependence: outcomes after Kasai portoenterostomy deteriorate sharply beyond the first two to three months of life, and the incidence in Asian populations is higher than in the West.[6,7] That 5 of our 34 infants already had established cirrhosis at first biopsy is therefore a sobering observation, and echoes the recurring theme of delayed referral in resource-constrained settings, and the wider difficulty of achieving timely recognition that continues to define this disease.[21]

Beyond infancy, Wilson disease emerged as the single commonest aetiology, at 14% of the whole cohort and 21.2% of children over one year. This closely mirrors the 21.6% reported by Samanta et al from Kolkata,[10] and the 16–22% range described in other South Asian series,[11,22] a frequency substantially higher than in European cohorts. Consanguinity, founder effects in the ATP7B gene and a low threshold for ceruloplasmin testing plausibly all contribute. Because effective chelation exists and untreated disease is fatal, this prevalence argues for screening every Indian child above three years presenting with unexplained chronic liver disease, as the ESPGHAN position paper recommends.[3] Our histology supports one caveat in that document: copper-associated protein was demonstrable in only 12 cases, so a negative rhodanine stain cannot exclude the diagnosis.

Autoimmune hepatitis accounted for 13% of cases, in keeping with the 10.8% of Samanta et al[10] and with the recognition that juvenile autoimmune liver disease is diagnosed more often than in the past, through both greater awareness and the relative decline of viral disease.[8,23] Indian paediatric experience has documented the same trend.[24] The plasma cell-rich interface hepatitis we observed is supportive rather than pathognomonic and requires integration with autoantibody and IgG data, as current guidance emphasises.[25] Chronic hepatitis B, at 8%, was far less frequent than the 24% reported by Hanif et al from Pakistan,[22] plausibly reflecting the maturation of universal infant immunisation in the interval.

The central methodological question this study addresses is whether biopsy justified itself. It did so in 24% of cases, where histology refined or overturned the clinical impression, most often in the diagnostically treacherous separation of biliary atresia from idiopathic neonatal hepatitis and in the reassignment of cryptogenic cirrhosis to a treatable metabolic or autoimmune cause. This is a more favourable verdict than that of Samanta et al, who concluded that careful senior clinical assessment could obviate biopsy in 78.3% of children.[10] The two positions are reconcilable: biopsy is dispensable in the majority precisely because clinical evaluation performs well, yet the minority in whom it changes the diagnosis are disproportionately those with treatable disease, where the cost of error is high. A residual cryptogenic rate of 10% despite full evaluation, comparable to the 13.5% inconclusive rate reported in that series, marks the current limit of morphology-based diagnosis and identifies the group in whom next-generation sequencing panels are likely to yield most.[2].

CONCLUSION

Chronic liver disease in infants and children encompasses a wide aetiological spectrum whose composition changes decisively with age. In the first year of life it is dominated by extrahepatic biliary atresia and the intrahepatic cholestatic

disorders, whereas beyond infancy metabolic and autoimmune causes, led by Wilson disease and autoimmune hepatitis, predominate. Advanced fibrosis was already present in more than half of the children at first biopsy, indicating substantial diagnostic delay. Liver biopsy, supported by a targeted panel of special stains and immunohistochemistry, confirmed the clinical impression in about two-thirds of cases and refined or altered it in a further quarter, most often in favour of a treatable diagnosis. Histopathology therefore retains a decisive role in the evaluation of the child with chronic liver disease, and a low threshold for biopsy is justified wherever the aetiology remains unresolved after first-line investigation.

Limitations: This was a single-centre study with a modest sample size and an inherent referral bias, since only children considered to require biopsy were enrolled; the true population spectrum of paediatric chronic liver disease is therefore not fully represented. Genetic confirmation by sequencing was not available for all suspected monogenic disorders, and the cross-sectional design precluded assessment of outcome.

Recommendations: Multicentre studies incorporating molecular diagnostics are needed to define the national spectrum more precisely and to resolve the cryptogenic group. Given the frequency of Wilson disease observed here, screening for it should be routine in every child above three years presenting with unexplained chronic liver disease, and sustained efforts towards earlier recognition of neonatal cholestasis remain a public health priority.

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