

Original Article



Autoimmune Sclerosing Cholangitis in Children: A Prospective Case-Control Study

Nagendra Kumar,¹ Ujjal Poddar ,¹ Rajnikant Yadav ,² Hira Lal,² Krushna Pani,³ Surender Kumar Yachha,¹ Anshu Srivastava,¹ and Rakesh Pandey³

¹Department of Pediatric Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

²Department of Radiodiagnosis, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

³Department of Pathology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

OPEN ACCESS

Received: Mar 24, 2020

1st Revised: Aug 9, 2020

2nd Revised: Sep 7, 2020

Accepted: Nov 6, 2020

Correspondence to

Ujjal Poddar

Department of Pediatric Gastroenterology,
Sanjay Gandhi Post Graduate Institute of
Medical Sciences, Lucknow-226014, Uttar
Pradesh, India.

E-mail: ujjalpoddar@hotmail.com

Copyright © 2021 by The Korean Society of
Pediatric Gastroenterology, Hepatology and
Nutrition

This is an open-access article distributed
under the terms of the Creative Commons
Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>)
which permits unrestricted non-commercial
use, distribution, and reproduction in any
medium, provided the original work is properly
cited.

ORCID iDs

Ujjal Poddar

<https://orcid.org/0000-0001-5277-4401>

Rajnikant Yadav

<https://orcid.org/0000-0002-6955-850X>

Conflict of Interest

The authors have no financial conflicts of
interest.

ABSTRACT

Purpose: In children overlap of autoimmune hepatitis (AIH) and primary sclerosing cholangitis is labelled as autoimmune sclerosing cholangitis (ASC). The only prospective pediatric study showed a high prevalence of ASC by using endoscopic retrograde cholangiopancreatography. Aims of our study were to find the prevalence of ASC by using magnetic resonance cholangiography (MRC) in AIH and in non-AIH cirrhosis and to compare clinical presentation and outcome of AIH and ASC.

Methods: Prospectively we did MRC in 38 children with AIH (cases) and 19 disease controls (Wilson disease). Multiple biliary strictures with proximal dilatation on MRC were taken as definitive changes of ASC. Detail clinical, laboratory parameters, liver histopathology and treatment outcome were recorded.

Results: The median age of cases was 11.5 (3–18) years, 22 (57.9%) were girls and 28 (73.7%) were diagnosed as type 1 AIH. MRC was done in 11 children (28.9%) at the time of diagnosis and in 27 (71.1%) after a median follow-up of 2.5 (0.3–10) years. Abnormal MRC changes were seen in 14/38 (36.8%) of AIH and 8/19 (42.1%) of controls. However, definite changes of ASC were present in four (10.5%) children in AIH and none in controls. None of the clinical, laboratory, histological parameters and treatment response were significantly different between ASC and AIH groups.

Conclusion: The prevalence of ASC in children with AIH was just 10.5%. We suggest MRC in select group with cholestatic features, inflammatory bowel disease and in those who showed poor response to immunosuppression instead of all children with AIH.

Keywords: Autoimmune sclerosing cholangitis; Autoimmune liver disease; Autoimmune hepatitis; Magnetic resonance cholangiography

INTRODUCTION

Autoimmune liver disease encompasses autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) and ‘overlap syndromes’ of AIH with PBC or PSC [1]. However, in children only AIH-PSC overlap syndrome, also known as ‘autoimmune sclerosing cholangitis’ (ASC), has been recognized [2]. The early recognition of this overlap syndrome is important for management as well as for prognosis. It is often

difficult to identify AIH-PSC in children due to overlapping clinical presentations, similar auto-antibody pattern and histopathology. Diagnosis of sclerosing cholangitis (SC), largely depends on cholangiographic documentation of single or multiple strictures with dilatation of biliary tract [3]. The reported prevalence of AIH-PSC overlap in adults is 1.7–10% in AIH [4,5]. However, the prevalence of ASC in children is reported to be much higher (20–49%) [3,6]. In a study of 55 children with AIH Gregorio et al. [3], showed changes of SC in 27 (49.1%) cases on cholangiogram and authors concluded that both AIH and ASC are spectrum of the same disease. On the contrary, 20–35% cases of PSC in children had features of AIH [7–10] and the authors postulated that the manifestations of PSC in children is skewed towards hepatic presentation instead of cholestatic presentation as is seen in adults [10].

The guidelines of American Association for the Study of Liver Disease (AASLD) as well as the clinical practice guidelines of European Association for the Study of the Liver recommend, “all children with AIH should undergo cholangiographic studies to exclude PSC” [11,12]. Recently, European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) hepatology committee's position statement also recommend cholangiographic studies in all children with AIH [13]. These recommendations are based on that study by Gregorio et al. [3], in which cholangiography was performed using invasive techniques such as endoscopic retrograde cholangiography (ERC) or percutaneous transhepatic cholangiography [3]. Currently, non-invasive technique like magnetic resonance cholangiography (MRC) with high sensitivity (84%) and accuracy (84%) has become the investigation of choice for evaluation of biliary diseases in children [14]. There is scarcity of study on the prevalence of SC in children with AIH using MRC. Aims of our study were; (A) to find out the prevalence of ASC by using MRC in children with AIH; (B) to compare the clinical features and treatment outcome of children with AIH and ASC, and (C) to compare the MRC changes in AIH and in non-AIH, non-biliary causes of cirrhosis.

MATERIALS AND METHODS

In this prospective case-control study, we performed MRC in 39 children with AIH (one child was excluded later due to poor quality of MRC images) and in 19 children with non-autoimmune, non-cholestatic causes of chronic liver disease who served as controls from April 2015 to January 2017. The study was carried out at the department of Pediatric Gastroenterology, Sanjay Gandhi Institute of Medical Sciences, Lucknow, India. We included children (≤ 18 years of age) diagnosed to have AIH based on simplified diagnostic criteria (probable when AIH score ≥ 6 and definite when AIH score ≥ 7) [15]. We excluded children with seronegative AIH, already established SC and those cases who had contraindication for MRC or were unwilling or uncooperative. All children in control arm ($n=19$), were diagnosed as Wilson disease as per AASLD management guidelines [16]. Children with AIH and controls were assessed for Child-Pugh status [17].

Clinical features and laboratory details at the time of diagnosis of all children were retrieved from our electronic data-base and recorded in a proforma. Children with AIH were treated with prednisolone (2 mg/kg/day) induction followed by low dose steroids plus azathioprine (1–2 mg/kg/day) as maintenance therapy. All children were followed-up regularly with clinical and biochemical parameters (monthly until remission was achieved and then 3 monthly). Second line immunosuppression therapy (cyclosporin A or mycophenolate mofetil) was considered when there was failure to achieve remission with first line therapy. Clinical and

laboratory details at diagnosis and clinical course while on therapy between AIH and ASC were compared. Similarly, liver histopathology was looked at to find out any differences between AIH and ASC.

Ethical statement

The study was approved by institutional ethical committee (IEC code 2015-54-DM-84) and written informed consent was obtained from either parent.

Magnetic resonance cholangiography

The MRC was done by using a 3-Tesla magnetic resonance system which has eight-channel phased-array torso coil (GE Signa HDxt 3.0T; General Electric Medical Systems, Milwaukee, WI, USA). Intravenous sedation was used in uncooperative children. To obtain maximum intensity projection and multiplanar reformatted images, post-processing of image data was done. Two experienced radiologists (R. Y. and H. L.) who were blinded to the clinical and histological features of patients, reviewed three-dimensional reconstructed cholangiograms and whenever there was a dispute, the definitive decision was taken by consensus. Intrahepatic biliary ducts were considered dilated when the diameter of intrahepatic ducts was greater than central duct. The MRC changes such as multiple and diffuse intrahepatic and/or extrahepatic bile duct strictures associated biliary dilatation were taken as *definite feature of SC*. On the contrary, changes such as just ductal irregularity, mild focal narrowing without upstream dilatation were considered as *probable changes of SC*. The changes in liver morphological features were part of liver Magnetic Resonance Imaging (MRI). Confluent fibrosis was defined as a region of amorphous fibrosis of >2 cm in diameter which had hyperintense signal on T2-weighted image and hypointense signal on T1-weighted image.

Histopathological assessment

Liver biopsies were analysed by two pathologists (K.P and R.P), who were blinded to the clinical and radiological data. The severity of the necro-inflammatory process was semi-quantitatively graded on a scale of 0 to 4 (0=absent; 1=minimal; 2=mild; 3=moderate; 4=severe), and separate scores were obtained for portal tract inflammation, lobular/nodular activity, and interface hepatitis [18]. Fibrosis was staged as per METAVIR staging system on a 0–4 scale as follows: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis and few septa; F3, numerous septa without cirrhosis; F4, cirrhosis [19].

Statistical analysis

The data was analyzed by using SPSS for Windows, Version 15.0. (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as median with range and categorical data as number with percentages. Mann-Whitney U-test or Wilcoxon-Rank sum test for comparison of continuous variables and for categorical variables, Chi-square or Fisher's exact tests were used. A *p*-value of <0.05 was considered statistically significant.

RESULTS

The median age of 38 children with AIH was 11.5 (range, 3–18) years and 22 (57.9%) were girls. The majority (n=28, 73.7%) were diagnosed as type 1 AIH, 21 children (55.3%) had definite and 17 (44.7%) had probable AIH. MRC was done in 11 children (28.9%) at the time of diagnosis and remaining 27 (71.1%) it was done after a median follow-up of 2.5 (range, 0.3–10) years. The majority of children (n=23, 60.5%) with AIH were in either Child B (n=11)

or Child C (n=12) category of cirrhosis. None had a history suggestive of cholangitis or inflammatory bowel disease. The median age of 19 children in control group was 10 (range, 5–17) years and 17 were males, all were diagnosed as Wilson's disease and 14 (73.7%) were in either Child B or Child C category of cirrhosis.

MRI of liver and MRC findings between AIH and controls are shown in **Table 1**. In AIH group, four children (10.5%) had strictures with upstream dilatation in intrahepatic (n=2) and extra hepatic (n=2) bile ducts, consistent with *definite ASC* (**Fig. 1**). Another 10 children (26%) had intrahepatic or extra hepatic changes like contour irregularity and focal narrowing without upstream dilatation and were considered as *probable SC* (**Fig. 2**). The changes of *probable SC* were also seen in 8 controls (42%), and none had features of definite ASC. There were no significant differences in imaging characteristics (parenchymal and ductal) between AIH and control group (**Table 1**). MRC detection of ASC was not different whether it was done at the time of diagnosis or on follow-up [1/11 (9.1%) vs. 3/27 (11.1%) respectively; $p=1.00$]. None had significant pericholedochal collaterals in cross section imaging. The presence of probable ASC was not different in various stages of fibrosis.

Clinical and laboratory features at the time of diagnosis between autoimmune sclerosing cholangitis and autoimmune hepatitis

Clinical parameters at diagnosis are summarised in **Table 2**. Among four children with definite ASC, three presented as chronic liver disease and one child had acute hepatitis like presentation. All ASC patients had definite (as per simplified diagnostic criteria by International Autoimmune Hepatitis Group and type 1 AIH. There were no statistically significant differences in clinical features, timing of MRC and Child-Pugh score between ASC and AIH group. None of the laboratory parameters such as alkaline phosphatase, alkaline phosphatase to aspartate aminotransferase ratio (AST), gamma-glutamyl transpeptidase (GGT) or GGT to AST ratio were statistically different between groups.

Histological findings

Liver biopsy was available for all 4 children with ASC and 29 children of AIH without ASC. None of inflammatory activity including portal tract inflammation, fibrosis, rosette formation, giant cell formation was significantly different between the groups. Almost half (n=14, 48%) of the children with AIH without imaging evidence of SC had bile ductular

Table 1. Comparison of MRI and MRC findings between children with AIH and controls

MRI/MRC findings	AIH (n=38)	Controls (n=19)	p-value
Liver parenchymal heterogeneity	24 (63.2)	17 (89.5)	0.059
Surface irregularities	22 (57.9)	14 (73.7)	0.383
Confluent fibrosis	5 (13.2)	3 (15.8)	1.000
Atrophy	21 (55.3)	12 (63.2)	0.836
Left	7	3	
Right	13	9	
Both	1	0	
Intrahepatic duct changes	13 (34.2)	6 (31.6)	
Ductal irregularity	4 (10.5)	2 (10.5)	1.000
Focal narrowing (single or multiple)	7 (18.4)	4 (21.1)	1.000
Multiple stricture with dilatation (beaded appearance)	2 (5.3)	0 (0.0)	0.548
Extra hepatic duct changes	7 (18.4)	5 (26.3)	
Mild focal narrowing (single or multiple)	5 (13.2)	5 (26.3)	0.275
Single and multiple stricture with dilatation	2 (1 each; 5.3)	0 (0.0)	0.548

Values are presented as number (%) or number only.

MRI: magnetic resonance imaging, MRC: magnetic resonance cholangiogram, AIH: autoimmune hepatitis.

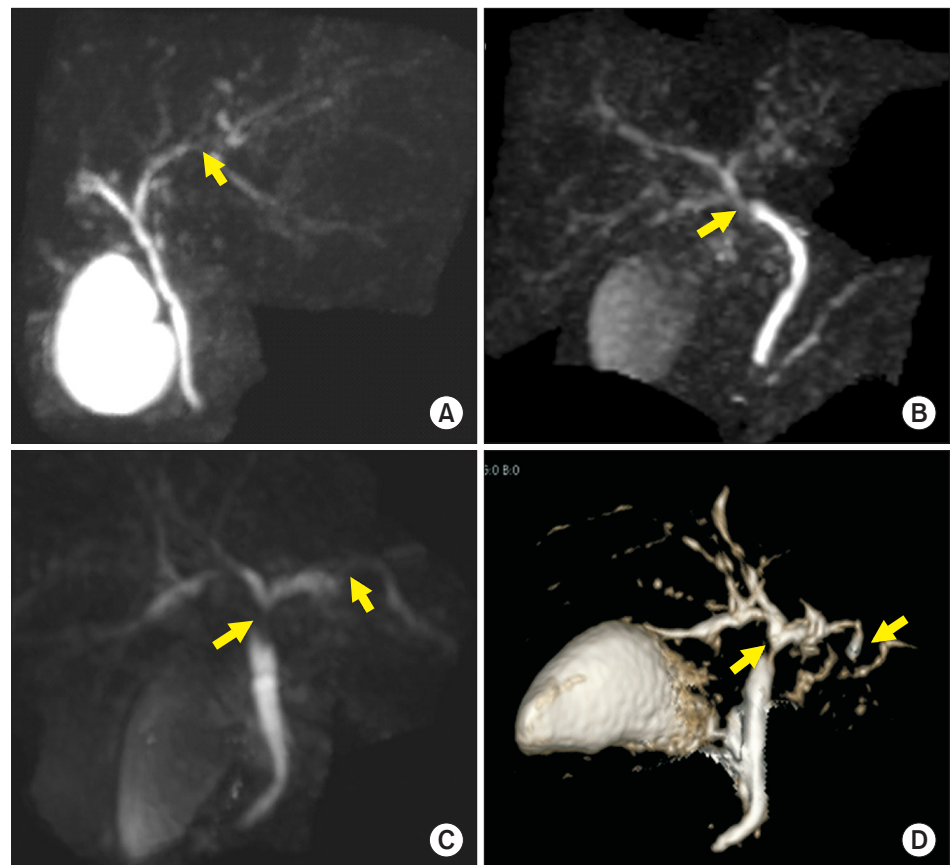


Fig. 1. Magnetic resonance cholangiography suggesting definite changes of SC (arrows). (A) A 7-year-old girl with lower CBD stricture with upstream dilatation. (B) A 16-year-old girl with segmental short strictures at right and left hepatic duct confluence. (C) A 16-year-old girl with multiple strictures in intrahepatic left hepatic duct, right anterior sectorial duct, right posterior sectorial duct (D) 14-year-old boy with short CBD stricture with LHD dilatation. CBD: common bile duct, LHD: left hepatic duct.

proliferation and destructive or non-destructive cholangitis. Similarly, two children (50%) with ASC had similar changes. There was no significant difference in bile ductular proliferation and cholangitis between the ASC and AIH group. None had peri-ductular concentric fibrosis or duct loss. Rectal biopsy in children with ASC (n=4), did not show any evidence of inflammatory bowel disease (IBD).

Clinical course between children with autoimmune hepatitis and autoimmune sclerosing cholangitis

Children with ASC were on immunosuppressive therapy for a median duration of 54 (range, 38–89) months and AIH group (n=24) for 29.5 (range, 4–125) months. None in ASC group required second line immunosuppression while three children in AIH group required mycophenolate mofetil and two required cyclosporine A. Remission was achieved in all with ASC and while only 61.8% (n=21/34) children with AIH had normal transaminases ($p=0.277$). However, time taken for normalisation of AST/ALT was longer in ASC group than AIH group in whom there was complete response [median 38 (27–48) vs. 10.5 (1–34) months, $p=0.03$]. In ASC group, only one patient had single relapse while on therapy, while AIH group had eight relapses in six patients ($p=0.439$).

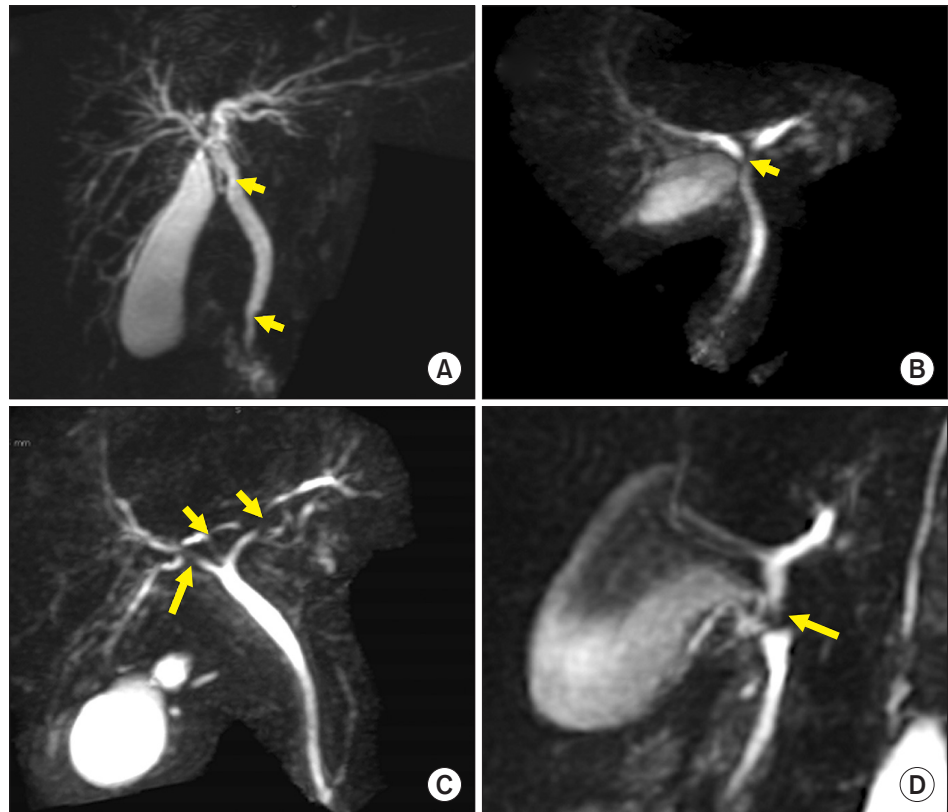


Fig. 2. Magnetic resonance cholangiography suggesting of probable changes of SC (arrows). (A) A 9-year-old girl with AIH showing mild focal narrowing at intrahepatic left hepatic duct system. (B) A 14-year-old boy with AIH showing mild focal narrowing in common hepatic duct. (C) A 16-year-old boy with Wilson's disease showing focal strictures at left hepatic duct and near primary confluence (D) volume rendering picture of image (C).

Table 2. Comparisons of demographic and clinical features at diagnosis between ASC and AIH

Clinical features	ASC (n=4)	AIH (n=34)	p-value
Median age at diagnosis (yr)	9.4 (7-11)	8 (1.1-17)	0.806
Females	3	19	0.624
Prolonged acute hepatitis	1 (25.0)	3 (8.8)	0.377
Chronic liver disease	3 (75.0)	27 (79.4)	1.000
Asymptomatic transaminasemia	0 (0.0)	2 (5.9)	0.499
Acute liver failure	0 (0.0)	2 (5.9)	0.499
Type 1 AIH	4 (100.0)	24 (70.6)	0.556
Definite AIH	4 (100.0)	17 (50.0)	0.024
Jaundice	3 (75.0)	25 (73.5)	1.000
Pruritus	0 (0.0)	3 (8.8)	0.404
Ascites	2 (50.0)	10 (29.4)	0.577
Variceal bleeding	0 (0.0)	4 (11.8)	0.676
Encephalopathy	0 (0.0)	3 (8.8)	1.000
Hepatomegaly	4 (100.0)	28 (82.4)	1.000
Splenomegaly	3 (75.0)	27 (79.4)	0.841
Associate autoimmune disorders	2	1	0.305
Celiac disease	0	1	
Raynaud's phenomena	1	0	
Arthralgia and skin with rash	1	0	
MRC at diagnosis	1 (25.0)	10 (29.4)	1.000
MRC in follow-up on immunosupresion	3 (75.0)	24 (70.6)	
Child-Pugh A	2 (50.0)	13 (38.2)	0.437
Child-Pugh B	2 (50.0)	9 (26.5)	
Child-Pugh C	0 (0.0)	12 (35.3)	

Values are presented as median (Interquartile range), number only, or number (%).

ASC: autoimmune sclerosing cholangitis, AIH: autoimmune hepatitis, MRC: magnetic resonance cholangiography.

DISCUSSION

This is the first prospective study of using MRC to find the prevalence of ASC in children with AIH and we found it to be just 10.5%, which is much less than the reported 50% figure but is same as has been reported in adults. Clinically, biochemically and histologically children of AIH with ASC and without ASC were indistinguishable. Response to immunomodulation therapy was also similar except the group with ASC required longer therapy to achieve remission.

The prevalence of ASC in our study was similar to the figure reported in adult studies [4,5]. Abdalian et al. [4] in their study of 79 adult patients of AIH showed evidence of ASC on MRC in 8 (10.1%) of patients. In another study, Lewin et al. [5] found only one of 59 (1.7%) adults with AIH having definite evidence of SC on MRC. On contrary to our observation, study by Gregorio et al. [3] in their study of 55 children with AIH showed ASC mainly by endoscopic retrograde cholangiopancreatography in half of the children. IBD was diagnosed in 44% of children with ASC. In a retrospective study of 134 children with AIH, MRC was done during follow-up in 36 children when there was a poor response to immunosuppressive therapy or patient developed cholestatic features. Among these select group of children, 28 (77.8%) showed evidence of ASC. The overall prevalence of ASC was 20.9% [6]. The prevalence of ASC in our study was low as we have studied a non-select group of children and did not preferentially included those cases who had high probability of having ASC such as children with cholestatic features, IBD or poor response to therapy as shown by Rodrigues et al. [6] Other reasons could be biological differences in patient population (Asian vs. Caucasian) and the stage of the disease in our population. However, it is highly unlikely that low prevalence of ASC in our study is due to milder form of AIH cases in whom we have done MRC as the severity of liver disease (AIH) in our study group was more than the study population of Gregorio et al. [3]. In our study 23 of 37 (62.2%) had advanced liver disease (Child-Pugh class B or C) while 34.5% children (19 of 55) studied by Gregorio et al. [3] had milder disease as they had no history of jaundice and their liver disease was picked up on detecting abnormal liver function tests or hepatosplenomegaly.

Although direct cholangiogram such as ERC is the gold standard in diagnosing SC, in view of its non-invasive nature and no radiation hazards, MRC has become the investigation of choice in children as well as in adults. A position statement from the international PSC study group has recently recommended that magnetic MRCP should be the first diagnostic imaging in patients with suspected SC [20]. Berstad et al. [21] have compared MRC with ERC which was done within 48 hours in 66 patients, and the accuracy of MRC was shown to be comparable to ERC (83% vs. 85% respectively). A meta-analysis [22] also suggested high sensitivity (86%) and specificity (94%) of MRC for diagnosing PSC. Like in adults, pediatric study also showed good sensitivity and accuracy (84%) of MRC in diagnosing PSC [4,5]. However, unlike adult studies on AIH-PSC overlap, none of the pediatric studies have prospectively used MRC for detection of SC in children with AIH [4,5].

In our study, mild focal narrowing and contour irregularity without proximal dilatation were seen in 26% of AIH cases and in 42% of controls. We believe, these are non-specific changes related to chronic liver disease as they were found in chronic liver disease of non-AIH as well. Rohrmann et al. [23] did ERC in 38 adults with cirrhosis and showed a high incidence of abnormal ductal caliber, multiple focal stenosis (58%), decreased arborisation and pruning (65%) and suggested that these changes are nonspecific and seen in cirrhosis of any etiology. Lewin et al. [5] did MRC in 59 adults with AIH and 27 with non-AIH

cirrhosis. They documented presence of intrahepatic bile duct irregularities and mild focal narrowing both in AIH (24%) and non-AIH cirrhosis (59%) groups. In-fact, fibrosis score (as per histopathology) was the only independent parameter associated with these changes. However, we could not demonstrate similar effect of fibrosis grade (based on histopathology) on these non-specific biliary changes.

There was no difference in clinical presentation between ASC and AIH group in our study. Similar observation has been reported both in children as well as in adults [3,6]. We found considerable similarity in liver function tests between the groups. Though the previous study on ASC in children documented ALP/AST ratio to be significantly high in children with ASC [3], we did not find any significance difference in our study and that may be because of smaller number of ASC cases.

In our study, there was no difference in inflammatory and fibrotic changes on histology between the groups. Interestingly, despite having no cholangiographic or biochemical evidences of SC, histopathological evidence of destructive/non-destructive cholangitis were seen equally in almost half of the cases in both groups. Czaja and Carpenter [24] systematically evaluated 84 adults with AIH and documented destructive/non-destructive changes of cholangitis in liver biopsy in 16 (19%), none had ductopenia or peri-ductular concentric fibrosis. They managed to do ERC in six of them and none showed any changes of SC, suggesting thereby that cholangitis on histopathology is not a specific feature of either ASC or AIH.

Gregorio et al. [3] found no significant difference in time taken for normalisation of liver functions, however transplant-free survival was better in AIH than ASC. The estimated 10 years transplant free survival was 65% in ASC as compared to 100% in AIH ($p=0.001$). In a retrospective study, Rodrigues et al. [6] reported no difference in response to treatment or prognosis between AIH and ASC [6]. Even though relapses were more in the ASC group, there was no difference in the survival rate. In our study, time taken for normalisation was longer in ASC as compared to AIH, but there was no difference in complete biochemical remission rates between ASC and AIH, none of the children required any additional immunosuppressants in ASC.

There is a debate whether ASC and AIH are spectrum of the same disease or ASC is nothing but pediatric variant of PSC. There was no differences in clinical presentation between AIH and ASC in our as well as the study by Gregorio et al. [3]. Recently, Rodrigues et al. [6] also showed no difference in survival between ASC and AIH in their study of 134 cases. These findings may suggest ASC and AIH are the spectrum of same disease. Gregorio et al. [3] managed to do follow-up cholangiogram in 17 children; 9 of them had static disease and 8 showed progression despite being on immunosuppression. Progression of biliary changes in this subset of children with ASC who more often had associated IBD (44% vs. 18%, $p=0.03$), positive p-ANCA (74% vs. 36%, $p=0.009$) and low 10 years transplant-free survival than in children with AIH (65% vs. 100%), suggest that some of these children probably had pediatric variant of PSC.

Based on our observation and recent literature, it may not be justified to subject all children with AIH to MRC [4-6]. Considering all facts, we suggest MRC in children with AIH like in adults, may be done in only those with cholestatic manifestations, or associated IBD (at diagnosis or during follow-up) and in children who do not show adequate response to immunosuppression.

The main limitation of our study is small sample size. We got only four children in the ASC group and that has made it difficult to interpret comparison. It is likely that we did not get any difference in clinical, biochemical, histological features and treatment outcome between ASC and AIH due to small number of ASC cases. We could not do MRC at diagnosis in all children. However, it has been shown that treatment (immunosuppressive) for AIH does not alter the cholangiographic changes [3]. Hence, it is unlikely that the prevalence of ASC would have been different had we do MRC at diagnosis in all cases.

In conclusion, definite feature of ASC is uncommon in children with AIH and seen in just 10.5% of cases. We suggest MRC in a select group of children with cholestatic features, IBD and in those who showed poor response to immunosuppression, instead of all children with AIH.

ACKNOWLEDGEMENTS

This paper was presented as oral paper in the 51st Annual meeting of European Society of Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) at Geneva, Switzerland, from 9–12 May 2018.

REFERENCES

1. Boberg KM, Chapman RW, Hirschfield GM, Lohse AW, Manns MP, Schrupf E; International Autoimmune Hepatitis Group. Overlap syndromes: the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue. *J Hepatol* 2011;54:374-85.
[PUBMED](#) | [CROSSREF](#)
2. Mieli-Vergani G, Vergani D. Paediatric autoimmune liver disease. *Arch Dis Child* 2013;98:1012-7.
[PUBMED](#) | [CROSSREF](#)
3. Gregorio GV, Portmann B, Karani J, Harrison P, Donaldson PT, Vergani D, et al. Autoimmune hepatitis/sclerosing cholangitis overlap syndrome in childhood: a 16-year prospective study. *Hepatology* 2001;33:544-53.
[PUBMED](#) | [CROSSREF](#)
4. Abdalian R, Dhar P, Jhaveri K, Haider M, Guindi M, Heathcote EJ. Prevalence of sclerosing cholangitis in adults with autoimmune hepatitis: evaluating the role of routine magnetic resonance imaging. *Hepatology* 2008;47:949-57.
[PUBMED](#) | [CROSSREF](#)
5. Lewin M, Vilgrain V, Ozenne V, Lemoine M, Wendum D, Paradis V, et al. Prevalence of sclerosing cholangitis in adults with autoimmune hepatitis: a prospective magnetic resonance imaging and histological study. *Hepatology* 2009;50:528-37.
[PUBMED](#) | [CROSSREF](#)
6. Rodrigues AT, Liu PM, Fagundes ED, Queiroz TC, de Souza Haueisen Barbosa P, Silva SL, et al. Clinical characteristics and prognosis in children and adolescents with autoimmune hepatitis and overlap syndrome. *J Pediatr Gastroenterol Nutr* 2016;63:76-81.
[PUBMED](#) | [CROSSREF](#)
7. Miloh T, Arnon R, Shneider B, Suchy F, Kerker N. A retrospective single-center review of primary sclerosing cholangitis in children. *Clin Gastroenterol Hepatol* 2009;7:239-45.
[PUBMED](#) | [CROSSREF](#)
8. Deneau M, Jensen MK, Holmen J, Williams MS, Book LS, Guthery SL. Primary sclerosing cholangitis, autoimmune hepatitis, and overlap in Utah children: epidemiology and natural history. *Hepatology* 2013;58:1392-400.
[PUBMED](#) | [CROSSREF](#)
9. Batres LA, Russo P, Mathews M, Piccoli DA, Chuang E, Ruchelli E. Primary sclerosing cholangitis in children: a histologic follow-up study. *Pediatr Dev Pathol* 2005;8:568-76.
[PUBMED](#) | [CROSSREF](#)

10. Feldstein AE, Perrault J, El-Youssif M, Lindor KD, Freese DK, Angulo P. Primary sclerosing cholangitis in children: a long-term follow-up study. *Hepatology* 2003;38:210-7.
[PUBMED](#) | [CROSSREF](#)
11. Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, et al. Diagnosis and management of autoimmune hepatitis. *Hepatology* 2010;51:2193-213.
[PUBMED](#) | [CROSSREF](#)
12. European Association for the Study of the Liver. EASL Clinical practice guidelines: autoimmune hepatitis. *J Hepatol* 2015;63:971-1004.
[PUBMED](#) | [CROSSREF](#)
13. Mieli-Vergani G, Vergani D, Baumann U, Czubkowski P, Debray D, Dezsöfi A, et al. Diagnosis and management of pediatric autoimmune liver disease: ESPGHAN Hepatology Committee position statement. *J Pediatr Gastroenterol Nutr* 2018;66:345-60.
[PUBMED](#) | [CROSSREF](#)
14. Chavhan GB, Roberts E, Moineddin R, Babyn PS, Manson DE. Primary sclerosing cholangitis in children: utility of magnetic resonance cholangiopancreatography. *Pediatr Radiol* 2008;38:868-73.
[PUBMED](#) | [CROSSREF](#)
15. Hennes EM, Zeniya M, Czaja AJ, Parés A, Dalekos GN, Krawitt EL, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology* 2008;48:169-76.
[PUBMED](#) | [CROSSREF](#)
16. Roberts EA, Schilsky ML; American Association for Study of Liver Diseases (AASLD). Diagnosis and treatment of Wilson disease: an update. *Hepatology* 2008;47:2089-111.
[PUBMED](#) | [CROSSREF](#)
17. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973;60:646-9.
[PUBMED](#) | [CROSSREF](#)
18. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. *Hepatology* 1994;19:1513-20.
[PUBMED](#) | [CROSSREF](#)
19. Bedossa P, Poynard T An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology* 1996;24:289-93.
[PUBMED](#) | [CROSSREF](#)
20. Schramm C, Eaton J, Ringe KI, Venkatesh S, Yamamura J; MRI working group of the IPSCSG. Recommendations on the use of magnetic resonance imaging in PSC-A position statement from the International PSC Study Group. *Hepatology* 2017;66:1675-88.
[PUBMED](#) | [CROSSREF](#)
21. Berstad AE, Aabakken L, Smith HJ, Aasen S, Boberg KM, Schrupf E. Diagnostic accuracy of magnetic resonance and endoscopic retrograde cholangiography in primary sclerosing cholangitis. *Clin Gastroenterol Hepatol* 2006;4:514-20.
[PUBMED](#) | [CROSSREF](#)
22. Dave M, Elmunzer BJ, Dwamena BA, Higgins PD. Primary sclerosing cholangitis: meta-analysis of diagnostic performance of MR cholangiopancreatography. *Radiology* 2010;256:387-96.
[PUBMED](#) | [CROSSREF](#)
23. Rohrmann CA Jr, Ansel HJ, Ayoola EA, Silvis SE, Vennes JA. Endoscopic retrograde intrahepatic cholangiogram: radiographic findings in intrahepatic disease. *AJR Am J Roentgenol* 1977;128:45-52.
[PUBMED](#) | [CROSSREF](#)
24. Czaja AJ, Carpenter HA. Autoimmune hepatitis with incidental histologic features of bile duct injury. *Hepatology* 2001;34(4 Pt 1):659-65.
[PUBMED](#) | [CROSSREF](#)