Japanese Journal of Gastroenterology and Hepatology

Research Article

# Assessing the Severity of Advanced Intestinal Failure Associated Liver Disease in Children

**Legeret C[1*], Modin L[1], Beath S[1], Hartley J[1] and Gupte GL[1]**

[1]Department of Liver Unit (including small bowel transplantation), Birmingham Women's and Children's Hospital, Steel house Lane, B4 6NH Birmingham, UK

Received: 18 Feb 2020

Accepted: 16 Mar 2020

Published: 20 Mar 2020

**[*]Corresponding author:**

Corinne Legeret, Department of Liver Unit (including small bowel transplantation), Birmingham Women's and Children's Hospital, Steel house Lane, B4 6NH Birmingham, UK, Tel: +44 121 333 8255, E-mail: Corinne.Legeret@bluewin.ch

## 1. Abstract

**1.1. Background:** Gastro-Oesophageal Varices (GOV) in the presence of liver fibrosis along with splenomegaly on USS abdomen are used as surrogate markers of portal hypertension for grading intestinal failure associated liver disease (IFALD). The severity of IFALD determines the type of intestinal transplant performed. We report on grading severity of IFALD in children assessed at our Centre for intestinal transplantation.

**1.2. Methods:** From a cohort of children with IFALD, forty-nine were selected because they had simultaneous abdominal ultrasound (USS), Oesophago-Gastro-Duodenoscopy (OGD) and liver histology.

**1.3. Results:** In total, 40/49 children had splenomegaly of which 8 had GOV and 39 had fibrosis on liver biopsy. The presence of liver fibrosis was associated with splenomegaly ($p=0.03$) while this was not seen for GOV ($p=0.45$). Eight children with IFALD had no splenomegaly, no GOV and no fibrosis and required no further investigations to stage degree of liver disease. One patient, who had undergone splenectomy, had GOV.

**1.4. Conclusion:** Splenomegaly and liver fibrosis are common in children with IFALD, but gastro-oesophageal varices are uncommon and hence may not be a useful surrogate marker for assessing severity of IFALD in children.

**2. Abbreviations:** IFALD: Intestinal Failure-Associated Liver Disease; PN: Parenteral Nutrition; CLITx: Combined Liver and Intestinal Transplantation; ITx: Intestinal Transplantation; OGD: Oesophago-Gastro-Duodenoscopy; GOV: Gastro-Oesophageal Varices

**3. Keywords:** Children; Intestinal failure; Intestinal failure associated liver disease; Intestinal transplantation; Portal hypertension

## 4. Background

Intestinal failure-associated liver disease (IFALD) is a multi factorial liver disease initiated by long-term use of parenteral nutrition (PN) [1]. Transplant-free survival in patients, who do not achieve enteral autonomy, did improve over the last 15 years [2], but sometimes a Combined Liver and Intestinal Transplantation (CLITx) is the only life saving treatment. Staging of liver disease and severity of portal hypertension in irreversible Intestinal Failure (IF) determines type of transplant (isolated liver or CLITx) offered to children being assessed for Intestinal Transplantation (ITx).

Methods for assessment of portal hypertension in primary liver disease include: Abdominal ultrasound (spleen size), OGD (Gastro-Oesophageal Varices (GOV)), biomarkers and hepatic

fibrosis on liver biopsy. In current practice, the same methods are the recommended screening tools for assessment of portal hypertension in IFALD. The aim was to evaluate the reliability of these surrogate markers in the setting of children with IFALD referred for ITx assessment.

## 5. Methods

A single centre, retrospective review of children with IFALD who underwent assessment for ITx (September 2004 - December 2016). IFALD was defined as per position paper of the ESPGHAN working Group of Intestinal failure and Intestinal Transplantation

(1): Minimum one episode of a total bilirubin ≥100 μmol/L for ≥4 weeks in the absence of catheter related sepsis. Data collected: demographics, biochemical markers, size of liver and spleen on abdominal ultrasound, OGD and liver biopsy. Radiologists measured splenic span and reported according to age and height standards for splenomegaly in children (3) whether a splenomegaly war present or not. Paquet's classification was used for the grading of GOV (4). The fibrosis on liver biopsy was graded by histopathologist using the Ishak system (5), assigning it to the different Ishak stages (IS) of fibrosis: IS 0 (none), IS 1 (mild), IS 2 (mild-moderate), IS 3 (moderate), IS 4 (moderate-severe), IS 5 (severe), IS 6 (cirrhosis).

Statistical analyses were performed using STATA 13 (StataCorp LP, Texas). Clinical characteristics were analysed in a descriptive way. For pair wise comparison, chi square test was used for binary outcome variables and Fisher exact test was used for small samples. The unpaired t-test was used for continuous numerical outcome variables and Wilcoxon rank-sum test was used for non-normally distributed data. Statistical significance was defined as $p<0.05$.

## 6. Results

Of 300 children assessed for ITx, 110 fulfilled the criteria for IFALD (61 without simultaneous investigations were excluded) leaving 49 children (29 M, 20 F) included (Table 1). 40 had splenomegaly on USS, of which 39/40 had fibrosis (mild fibrosis n=17, moderate/severe fibrosis n=18, cirrhosis n=4), but only 8 children had GOV. Nine children had no splenomegaly, of which one did have GOV (a child with splenectomy) and 5 children did have fibrosis on liver biopsy (Table 2). Significantly more children with liver fibrosis had splenomegaly (22/40) than did children without splenomegaly (1/9) p=0.03. 9/49 patients had stomas (3/9 had varices and 6/9 had no varices); There was no significant difference in frequency of varices (p= 0.15) or presence of fibrosis (p= 1.0) between children with/without stoma (p=0.15).

A significant association between degree of fibrosis and bilirubin (mean bilirubin 64 μmol/L in none/mild fibrosis and 114μmol/L in patients with moderate/severe fibrosis [95% CI 12.8-46.0, p=0.001]) was found. No association was found between platelets in patients with none/mild fibrosis (mean levels 159-214x109/L) and in patients with moderate/severe fibrosis (149-210x109/L) [95% CI -29.2-7.9, p=0.3]) or pro thrombin time (mean of 13 sec. in patients with none/mild fibrosis, mean of 14-15 sec. in patients with moderate/severe fibrosis [95% CI -0.2-0.9, p=0.2]).

**Table 1:** Patient characteristics of 49 patients with IFALD, who had an OGD, a liver biopsy and an Ultrasound performed during admission.

| **Demographics n=49** | **Result** |
|---|---|
| Male | 29 (59%) |
| Age at assessment, median years (range) | 2.5 (0.4-15.9) |
| **Diagnosis** | |
| Short bowel syndrome | 24(49%) |
| Dysmotility | 19 (39%) |
| Primary mucosal disorder | 6 (12%) |
| **Abdominal ultrasound** | |
| Splenomegaly[1] | 40 (83%) |
| Hepatomegaly | 26 (53%) |
| Ascites | 2 (4%) |
| **Endoscopy** | |
| Varices | 8 (16%) |
| Grade I | 7 (14%) |
| Grade II | 0 |
| Grade III | 1 (2%) |
| **Liver biopsy** | |
| Fibrosis | 45/49 (92%) |
| No fibrosis | 4 (8%) |
| Mild | 22 (45%) |
| Moderate/severe | 23 (47%) |
| Data are presented as n (%) unless otherwise stated. | |
| [1]One patient had splenectomy. | |

**Table 2:** Co-relation of splenomegaly with gastro-oesophageal varices and co-relation of splenomegaly and gastro-oesophageal varices with liver fibrosis in 49 children with IFALD.

| | **Splenomegaly not present** | **Splenomegaly present** | | **P value** |
|---|---|---|---|---|
| Gastro-oesophageal varices present | 1 | 7 | 8 | |
| Gastro-oesophageal varices not present | 8 | 33 | 41 | |
| TOTAL | 9 | 40 | 49 | 1 |
| | **Liver fibrosis not present[1]** | **Liver fibrosis Present[2]** | | **P value** |
| Gastro-oesophageal varices present | 3 | 5 | 8 | |
| Gastro-oesophageal varices not present | 23 | 18 | 41 | |
| TOTAL | 26 | 23 | 49 | 0.4481 |
| Splenomegaly present | 18 | 22 | 40 | |
| Splenomegaly not present | 8 | 1 | 9 | |
| TOTAL | 28 | 23 | 49 | 0.0256 |
| Data presented as frequency (n) in 2x2 tables. | | | | |
| [1]Liver fibrosis absent or minor changes only. | | | | |
| [2]Liver fibrosis present: moderate or moderately severe. | | | | |

## 7. Transplant decisions

Of the 49 children who had USS abdomen, liver biopsy and OGD, 22/49 children had a transplantation (11 CLITx, 11 isolated small bowel). Of the 11 children receiving CLITx, the decision to include liver graft was made on the basis of clinical and laboratory parameters in addition to the investigations. 8/11 had moderate/severe fibrosis on biopsy. One child, despite only mild fibrosis on liver biopsy, developed a progressive increase of bilirubin and paraesophageal varices on endoscopic ultrasound and was considered for CLITx. 10/11 children who were listed for isolated ITx had no varices, 6/10 had splenomegaly, normal platelets and bilirubin and mild or moderate fibrosis. Hepatic Venous Wedge Pressure Gradient (HVWPG), which was normal, was performed in one child with moderate/severe fibrosis and that child had an isolated intestinal transplantation.

27/49 children did not have a transplant: 7/27 died on the transplant waiting list, 11/27 had irreversible IF but only had mild liver disease at the time of ITx assessment, were continued on PN and 9/27 were weaned from PN.

## 8. Discussion

Our study demonstrates that splenomegaly and fibrosis on liver biopsy are common findings in children with IFALD, but the degree of hepatic fibrosis is variable and presence of GOV on OGD is uncommon. There seems to be no correlation between the degree of hepatic fibrosis and the presence of GOV in our study.

Our data are in accord with those of Kaufman S et al who published similar findings in children with progressive IFALD and reported that GOV were unusual findings, compared to patients with primary liver disease and an anatomically normal gastrointestinal tract [6].

It is not surprising that splenomegaly on ultrasound in children with IF may not be specific for portal hypertension, as it might represent an inter current infection or fat overload, particularly in children on PN [1]. In our cohort of patients, a normal sized spleen in children with IFALD excludes severe liver disease.

Oesophageal varices were rarely seen in our cohort and lack of oesophageal varices on OGD may not exclude underlying portal hypertension as the majority of children had moderate/severe fibrosis on liver biopsy and two children had cirrhosis. Our group has documented the reason for lack of oesophageal varices in children with IF and also reported on the development of ectopic varices [7, 8]. In the present cohort of patients with IFALD, there was no significant difference in frequency of varices and/or presence of liver fibrosis between patients with and without stomas (Table 3).

**Table 3:** Characteristics of the 9 patients with stoma

| Patient | Medical background | Fibrosis | GOV | Splenomegaly |
|---|---|---|---|---|
| 1 | Intestinal pseudo-obstruction | - | - | - |
| 2 | Intestinal aganglionosis | Yes, mild | - | yes |
| 3 | Microvillus inclusion disease | Yes, moderate | - | yes |
| 4 | Short Bowel Syndrome | Yes,moderate | Yes, Grade I | yes |
| 5 | Long segment Hirschsprung's disease | Yes, mild | Yes, Grade I | yes |
| 6 | Intestinal pseudo-obstruction | Yes, mild | - | yes |
| 7 | Megacystis-microcolon-intestinal hypoperistalsis syndrome | Yes, mild | Yes, Grade I | splenectomy |
| 8 | Long segment Hirschsprung's disease | Yes, moderate | - | yes |
| 9 | Megacystis-microcolon-intestinal hypoperistalsis syndrome | Yes, moderate | - | yes |

In our study hepatic fibrosis was common, but the degree was highly variable, which can be attributed to non-uniform histological changes in the liver due to the patchy distribution seen in biliary pathologies [9, 10].

We acknowledge that our study is limited by its retrospective nature, selection bias, relatively small numbers and varices reported by visualization on OGD which can have a poor inter-observer correlation [11].

In summary, this report indicates that in patients with IFALD it was difficult to establish the diagnosis of portal hypertension on the basis of surrogate investigations. Since no individual test captures the full extent of IFALD, we recommend abdominal USS and measurement of spleen size in patients with IF as a primary screening tool. In children with irreversible IF and splenomegaly, further investigations to stage liver disease including liver biopsy, OGD +/-endoscopic USS should be undertaken. In cases where the clinical and laboratory assessment do not provide conclusive evidence, measurement of the Hepatic Venous Wedge Pressure Gradient (HVWPG) would be our recommended investigation as was useful in the child who had an isolated intestinal transplantation as detailed above. A report with our experience with HVWPG in children with IFALD is in preparation from our centre. Newer modalities of investigations (endoscopic USS, transient elastography of the liver) and non-invasive tests need to be validated for assessment of portal hypertension in children with IFALD.

## References

1. Lacaille F, Gupte G, Colomb V, D Antiga L, Hartman C, Hojsak I et al. Intestinal failure-associated liver disease: a position paper of the

ESPGHAN Working Group of Intestinal Failure and Intestinal Transplantation. J Pediatr Gastroenterol Nutr. 2015; 60: 272-83.

2. Fullerton B, Sparks E, Modi B et al. Enteral autonomy, cirrhosis and long term transplant-free survival in pediatric intestinal failure patients. Journal of Pediatric surgery. 2016; 51: 96.

3. Konuş OL, Ozdemir A, Akkaya A, Erbaş G, Çelik H, Işik S et al. "Normal liver, spleen, and kidney dimensions in neonates, infants, and children: evaluation with sonography," The American Journal of Roentgenology. 1998; 171: 1693-8.

4. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F et al. Paquet KJ Prophylactic endoscopic sclerosing treatment of the esophageal wall in varices -- a prospective controlled randomized trial. Endoscopy. 1982; 14: 4-5.

5. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F et al. Histological grading and staging of chronic hepatitis. J Hepatol. 1995; 22: 696-9.

6. Kaufman SS. Prevention of parenteral nutrition-associated liver disease in children. Pediatric Transplant 2002; 6: 37-42.

7. McKiernan PJ, Sharif K, Gupte GL The role of endoscopic ultrasound for evaluating portal hypertension in children being assessed for intestinal transplantation. Transplantation. 2008; 86: 1470-3.

8. Iyer VB, McKiernan PJ, Foster K et al. Stomal varices manifestation of portal hypertension in advanced intestinal failure-associated liver disease. J Pediatr Gastroenterol Nutr. 2011; 52: 630-1.

9. Ratziu V, Charlotte F, Heurtier A et al. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. Gastroenterology. 2005; 128: 1898-906.

10. Olsson R, Hagerstrand I, Broome U, Danielsson A, Järnerot G, Loof L et al. Sampling variability of percutaneous liver biopsy in primary sclerosing cholangitis. J Clin Pathol. 1995; 48: 933-5.

11. Wadhawan M, Dubey S, Sharma BC et al. Hepatic venous pressure gradient in cirrhosis: correlation with the size of varices, bleeding, ascites, and child's status. Dig Dis Sci. 2006; 51: 2264-9.