Intestinal failure-associated liver disease in surgical infants requiring long-term parenteral nutrition

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Abstract

Purpose: Our aim was to determine incidence, severity, and outcome, as well as predisposing factors and underlying diagnoses, of intestinal failure-associated liver disease (IFALD) in surgical infants requiring long-term parenteral nutrition (PN).

Methods: We retrospectively studied surgical infants receiving PN for at least 28 days for congenital or acquired intestinal anomalies over a 5-year period (January 2006 to December 2010). Intestinal failure-associated liver disease was defined as type 1 (early)—persistent elevation of alkaline phosphatase for 6 weeks or longer; type 2 (established)—additional elevated total bilirubin ($\geq 50 \mu\text{mol/L}$); and type 3 (late)—additional clinical signs of end-stage liver disease.

Results: Eighty-seven infants required PN for at least 28 days. Intestinal failure-associated liver disease occurred in 29 infants (33%). Intestinal failure-associated liver disease was managed medically in all but 2 patients who underwent intestinal elongation. None were referred for intestinal or liver transplant. Intestinal failure-associated liver disease has been reversed in 17 (59%) of cases to date. Sixty-one children receiving long-term PN (70%) have achieved enteral autonomy, whereas 12 (14%) require home PN. Severity of IFALD was significantly associated with duration of PN and female sex.

Conclusion: Intestinal failure-associated liver disease remains a fairly common but rarely life-threatening complication of intestinal failure in surgical infants. Intestinal failure-associated liver disease can be reversed in more than half of these children, and enteral autonomy was achieved in more than two thirds, even with minimal use of intestinal elongation. This is the first study to demonstrate an association between the severity of IFALD in surgical infants and female sex.

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including infections and liver disease [3-8]. Intestinal failure-associated liver disease (IFALD) has been reported in 40% to 60% of children requiring long-term PN [8-10]. Our aim was to determine incidence, severity, and outcome, as well as predisposing factors and underlying diagnoses, of IFALD in a recent series of surgical infants requiring long-term PN.

1. Methods

We report a retrospective single-centre cohort study of surgical infants receiving PN for at least 28 days during a recent 5-year period (January 2006 to December 2010). The study had institutional ethical approval. Intestinal failure-associated liver disease was identified and graded according to British Society of Paediatric Gastroenterology, Hepatology and Nutrition guidelines [11]. Briefly, this was defined as type 1 early IFALD—persistent elevation of alkaline phosphatase (ALP) greater than 1.5 times the upper limit of reference range for at least 6 weeks; type 2 established IFALD together with elevation of total bilirubin (>50 μmol/L), with a conjugated fraction of at least 50%; and type 3 late IFALD—elevated ALP, total bilirubin, and clinical signs of end-stage liver disease.

Management of PN was as described previously in a paper from our group describing IFALD in children of all ages from 2006 to 2009 [12]. This is a general review of 279 children with IFALD from our institution and includes data on 70 of the infants described in the current series. Briefly, PN was prescribed according to the Guidelines on Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition and the European Society for Parenteral and Enteral Nutrition [13]. The formulation was usually “tailor made” for the individual infant. The initial standard intravenous lipid emulsion used was a soya-based lipid (Intralipid 20%®; Fresenius Kabi, Runcorn, UK). The lipid was changed when ALP, alanine aminotransferase, or γ-glutamyl transferase levels were elevated to 1.5 times the upper limit of the reference range for more than 2 weeks, or conjugated bilirubin was more than 2 mg/dL (>50 μmol/L). In premature infants, the lipid was changed within a week of raised enzyme levels. Alternative lipids used were a medium chain triglyceride/long chain triglyceride mixture (Lipofundin®; B. Braun, Melsungen, Germany) or a lipid with medium chain triglyceride, long chain triglyceride, olive and fish oil (SMOF lipid®; Fresenius Kabi, Runcorn, UK). Enteral feed was introduced at the earliest possible opportunity and increased as tolerated.

Data collected included diagnosis, duration of PN, episodes of septicaemia (defined as growth of microorganisms from blood culture), and organisms cultured. Information on duration of PN was obtained from the pharmacy database, whereas data on number of blood cultures taken and results of culture were obtained from the pathology/microbiology database. Data are presented as median (range).

Data were compared using Fisher’s Exact test, Mann-Whitney test, χ2 test for trend, or ordinal regression analysis, which was used to determine risk factors for IFALD. A P value of .05 or less was considered significant.

2. Results

Eighty-seven (50 male, 57%) infants required PN for at least 28 days. Of these, 49 (56%) were born prematurely. Median age at start of PN was 27 (1-347) days, and the overall duration was 62 (28-310) days. Fifty-three infants (61%) experienced at least one episode of septicaemia. The underlying diagnoses were necrotising enterocolitis in 37 (43%), abdominal wall defects in 21 (24%), and congenital bowel obstruction in 25 (29%) (Table 1).

Intestinal failure-associated liver disease occurred in 29 infants (33%). These were graded as type 1 (n = 7), type 2 (n = 13), and type 3 (n = 9). Intestinal failure-associated liver disease was associated with longer PN duration (P = .002). IFALD was associated with female sex (overall [P = .04] and with trend for increasing severity [P = .006]; Fig. 1), and this association remained even after adjusting for gestational age, diagnostic group, age at start of PN, duration of PN, and presence of septicaemia (P = .02 by ordinal regression analysis). Although most infants with intestinal failure were male, most with type 2 or 3 IFALD were female. Unexpectedly, infants who experienced at least one episode of septicaemia were no more likely to develop IFALD than those who did not (P = 1.0). There was no association between prematurity or underlying diagnoses and development of IFALD.

Clinical outcomes at a median follow-up of 24 (5-62) months are summarised in Table 2. No patients were referred for intestinal or liver transplant, as they did not meet the relevant criteria. Intestinal failure-associated liver disease was managed medically in all, except 2 children who

<table>
<thead>
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<th>Table 1 Patient characteristics and diagnoses</th>
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<tr>
<td>Non-IFALD (n = 58)</td>
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<td>---------------------</td>
</tr>
<tr>
<td>Males</td>
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<tr>
<td>Age at start of PN (d)</td>
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<tr>
<td>Duration of PN (d)</td>
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<tr>
<td>Preterm</td>
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<tr>
<td>Septicaemia</td>
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<td>Necrotising enterocolitis</td>
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<td>Congenital bowel obstruction</td>
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<tr>
<td>Abdominal wall defect</td>
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<td>Other intestinal failure</td>
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Data are presented as mean (range). Comparisons are Mann-Whitney or Fisher’s Exact test as appropriate. NS indicates not significant.
underwent serial transverse enteroplasty procedures (one child died of sepsis and in the other, IFALD was reversed and the child achieved enteral autonomy after a period of home PN). To date, IFALD has been reversed in 17 infants (59%). Sixty-one (70%) children receiving long-term PN have achieved enteral autonomy, whereas 12 (14%) require home PN. There were 13 deaths overall (15%); 9 deaths were PN related (8 because of sepsis and 1 because of liver failure). Of the 13 deaths, 5 were in patients who developed IFALD. Of the 13 infants who died, 8 were born prematurely. Two of the others had congenital diaphragmatic hernia with severe pulmonary hypertension.

3. Discussion

This large retrospective study shows that IFALD remains a fairly common but rarely life-threatening complication of intestinal failure and long-term PN in surgical infants. Intestinal failure-associated liver disease can be reversed in more than half of these children, and enteral autonomy can be achieved in more than two thirds, even with very limited use of intestinal elongation. Mortality, both overall and PN-related, is similar in those infants with IFALD and those without; only one death was due to liver failure.

The 33% incidence of IFALD in our study is slightly lower than the 40% to 60% reported in other studies of hospitalised children requiring long-term PN, despite that surgical infants are noted to have a higher incidence of IFALD than other hospitalised children [8-10]. The finding that IFALD was not associated with sepsis is in contrast to a previous comparable study [14], but is in keeping with findings in the mixed medical/surgical cohort of children with IFALD with which the current group of surgical infants with IFALD overlaps [12]. This may be attributed to prompt treatment of sepsis with appropriate antibiotics and removal of central venous catheters when indicated. Alternatively, this may reflect differences in definition of IFALD, the current requires a persistent elevation of alkaline phosphatase, with or without elevated bilirubin, compared with previous definitions based purely on a single plasma bilirubin level (as used in the study by Beath et al. [14]), which may be transiently raised during an episode of sepsis.

In contrast to the wider mixed medical/surgical cohort of children with IFALD [12], we found no association of IFALD with prematurity, presumably because of the high numbers of term non-surgical children in the mixed cohort who are less likely to develop IFALD.

In this series, intestinal lengthening procedures, have been used in only two patients, precluding any conclusions as to the merits of this intervention. The role of these procedures in management of intestinal failure in infants should be evaluated in prospective studies and trials.

The finding that female sex was associated with development of IFALD is also in contrast to previous studies, some of which found no association between sex and development of IFALD [15-17], and two of which found an increased incidence of cholestasis among male infants on PN [18,19]. However, one of the latter studies was relatively small, included both surgical and nonsurgical infants, and included infants with much shorter duration of PN (some as short as 1 week). Furthermore, most cases had “mild cholestasis,” only one case of “severe cholestasis” [18]. The other study included surgical patients receiving PN for more than 1 week and defined PN-associated cholestasis as PN for at least 2 weeks with an elevated bilirubin [19]. These authors do not describe the severity of cholestasis (though it may be inferred that many such children would have a milder degree of cholestasis than children with IFALD as defined by the British Society of Paediatric Gastroenterology, Hepatology and Nutrition criteria, which require persistently deranged liver function tests for a 6-week period) and did not look for any association of sex with more severe cholestasis. The reason for the discrepancy between studies is not known but may be in part related to the difference in the length of PN; it is noteworthy that in our study, most patients receiving PN for longer than 28 days were male. There is a body of evidence that various steroid hormones influence the function and proliferation of cholangiocytes [20]. The finding of an association between female sex and severe IFALD in surgical infants warrants further investigation. Although previous papers have considered outcomes from IFALD, it is difficult to make meaningful comparisons because of the differences in definition of IFALD - a consensus staged definition as used in this paper may provide a useful benchmark for future investigations.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Patient outcomes</th>
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<tr>
<td></td>
<td>Total (n = 87)</td>
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<tr>
<td>Achieved enteral autonomy</td>
<td>61 (70%)</td>
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<tr>
<td>On home PN</td>
<td>12 (14%)</td>
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<tr>
<td>Deaths (overall)</td>
<td>13 (15%)</td>
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<tr>
<td>Because of PN</td>
<td>9 (10%)</td>
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<tr>
<td>Because of end-stage liver failure</td>
<td>1 (1%)</td>
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| Fig. 1  | Sex and severity of IFALD.
studies rather than widely varying definitions of cholestasis such as those based on a single plasma bilirubin level.

Acknowledgments

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References